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## Table of Contents.

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**ORIGINAL ARTICLES—** Page.

Radio-Active Iodine ($I^{131}$) and Protein-Bound Iodine in Thyroid Disorders, by J. P. Madigan and W. E. King .. .. .. .. .. .. .. .. 801
The Reason for Coronary Atheroma and Occlusion, by W. J. McCristal .. .. .. .. .. .. .. 814
Chemical Additions to Food as Factors Possibly Contributing to Disease, by R. M. W. Cunningham, Ph.C. .. .. .. .. .. .. .. .. .. 819

**REPORTS OF CASES—**

The Study of Electrolyte and Water Balance in a Case of Pink Disease, by Donald B. Cheek, M.D. 822

**REVIEWS—**

Parsons' Diseases of the Eye .. .. .. .. .. .. 827
Synthesis and Metabolism of Adrenocortical Steroids 827
Clinical Electrocardiography .. .. .. .. .. .. 827
The Quest for Youth .. .. .. .. .. .. .. .. 828
Human Neuroanatomy .. .. .. .. .. .. .. .. 828

**BOOKS RECEIVED** .. .. .. .. .. .. .. .. .. 828

**LEADING ARTICLES—**

Radical Operations of Surgery .. .. .. .. .. 829

**CURRENT COMMENT—**

Myelosclerosis .. .. .. .. .. .. .. .. .. 830
An Ætiology of Scleroderma .. .. .. .. .. 831
Diet and Coronary Disease .. .. .. .. .. .. 832
Pooled Plasma and Homologous Serum Jaundice .. 833
Acute Osteomyelitis .. .. .. .. .. .. .. .. 833

**ABSTRACTS FROM MEDICAL LITERATURE—**

Orthopædic Surgery .. .. .. .. .. .. .. .. 834
Pædiatrics .. .. .. .. .. .. .. .. .. .. 835

**SPECIAL ARTICLES FOR THE CLINICIAN—**

C. Asphyxia Neonatorum .. .. .. .. .. .. .. 836

**BRITISH MEDICAL ASSOCIATION NEWS—** Page.

Scientific .. .. .. .. .. .. .. .. .. .. 837

**OUT OF THE PAST** .. .. .. .. .. .. .. .. .. 841

**CORRESPONDENCE—**

Bronchiectasis with Normal Plain X-Ray Findings 841
Cortisone and Acute Rheumatism .. .. .. .. 841
Registration of Medical Practitioners in New South Wales .. .. .. .. .. .. .. .. .. 842
The Use of Muscle Relaxants in Electro-Convulsive Therapy .. .. .. .. .. .. .. .. 842

**UNIVERSITY INTELLIGENCE—**

The University of Sydney .. .. .. .. .. .. 842

**PUBLIC HEALTH—**

Infectious Diseases in Queensland .. .. .. .. 843
The Poliomyelitis Society .. .. .. .. .. .. 843

**DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA** .. .. .. .. .. .. .. 843

**NAVAL, MILITARY AND AIR FORCE—**

Appointments .. .. .. .. .. .. .. .. .. 844

**ROYAL AUSTRALASIAN COLLEGE OF SURGEONS—**

Final Fellowship Examination .. .. .. .. .. 844

**NOMINATIONS AND ELECTIONS** .. .. .. .. .. 844

**DEATHS** .. .. .. .. .. .. .. .. .. .. .. 844

**DIARY FOR THE MONTH** .. .. .. .. .. .. .. 844

**MEDICAL APPOINTMENTS: IMPORTANT NOTICE** .. 844

**EDITORIAL NOTICES** .. .. .. .. .. .. .. .. 844

## RADIO-ACTIVE IODINE ($I^{131}$) AND PROTEIN-BOUND IODINE IN THYROID DISORDERS.

By J. P. MADIGAN and W. E. KING,
*Melbourne.*

SUPPLIES of radio-active iodine (hereinafter $I^{131}$) became available for clinical trial in Melbourne in 1948. The opportunity was taken to use this new agent in investigating thyroid disorders. Later analysis of protein-bound iodine (hereinafter referred to as PBI) in blood plasma was possible. This review discusses experience with $I^{131}$ tracer studies and estimations of PBI in a group of patients with known or suspected thyroid disorders. In addition, the results of treating a small number of patients suffering from thyrotoxicosis or malignant disease of the thyroid with radio-active iodine are recorded.

Oddie and Scott (1949) have already reported on some of the preliminary work done in Melbourne from 1948 to 1950 to investigate the correlation of some of the physical indices associated with uptake and excretion of tracer doses of $I^{131}$ with clinical assessment of thyroid function. In this period 65 patients, comprising normal controls, cases of suspected or obvious hyperthyroidism or hypothyroidism and a few cases of malignant disease of the thyroid, were investigated. Concurrently, adequate measures for protection of personnel and equipment against radio-active contamination were arranged.

In 1950 a group including physicians, radiotherapists, physicists, a pathologist and a biochemist undertook to investigate certain aspects of thyroid disease. The chief aims were as follows: (i) Determination of the value of physical indices concerning uptake and excretion of tracer doses of $I^{131}$ as an indication of thyroid function. (ii) Determination of the value of PBI as an index of thyroid function. (iii) Critical comparison of the value of physical indices, PBI and basal metabolic rate estimations in the same group of patients compared to clinical assessment. (iv) Comparison of various physical indices to determine the most useful. (v) Clinical trial of $I^{131}$ as a therapeutic agent in selected cases of hyperthyroidism and carcinoma of the thyroid. (vi) Investigation of superior mediastinal "tumours" with tracer doses of $I^{131}$ in an endeavour to detect thyroid tissue if present. (vii) Establishment of a method of radio-autography.

### CLINICAL MATERIAL INVESTIGATED.

The majority of patients were referred to the group for investigation by other physicians. In general the type of cases investigated by tracer studies with $I^{131}$ and analysis of PBI were those in which the clinical diagnosis was not obvious. Common conditions seen included anxiety neuroses (often with an associated thyroid enlargement), cardiac disorders of uncertain ætiology, with or without a coexistent goitre, long-standing goitres suspected of becoming thyrotoxic, and several other equivocal conditions more fully discussed later.

It was realized at the outset that a survey of a large number of patients in whom thyroid function was unequivocal on clinical grounds alone would more readily give an idea of the accuracy of physical indices and PBI levels. However, cessation of medication with thiourylene drugs and iodide in such cases for a sufficient period to ensure the validity of these tests was an obstacle to employing such subjects. Moreover, it was considered that the tests would be more rigorously evaluated in a group of patients in which the clinical diagnosis was not so obvious.

From October, 1950, until May, 1953, a total of 152 tracer tests with $I^{131}$ was performed on 116 patients in whom thyroid function was investigated. These were eventually classified as follows: Group I: normal thyroid function (euthyroid). This group included 66 subjects who had a total of 72 tests. Group II: hyperthyroid function (thyrotoxic). This group included 45 subjects who had a total of 65 tests. Group III: hypothyroid function (myxœdema). This group included only three subjects who had a total of three tests.

Twelve tests carried out on eleven patients are not included in the analysis because of insufficient clinical data at the time of the test on which to interpret the true functional state of the thyroid. This difficulty occurred with a small number of patients—11. However, further tracer tests were performed on nine of these patients and are included in the foregoing series. Sometimes tracer tests were deliberately repeated on the one patient to assess progress, response to medical therapy or effects of ceasing administration of antithyroid drugs.

Therefore the analysis comprises a review of 140 tests on 114 patients. An additional 32 tests were performed on 32 patients in whom thyroid function was normal by all criteria to determine values for various physical indices on a group of normal controls. These are of no clinical interest and are not further discussed.

## Methods Employed.

### Preliminary Requirements.

Certain dietary factors, medications and special investigations are known to influence the results of PBI and the uptake of $I^{131}$ in the thyroid gland. Consequently, erroneous impressions of thyroid function can be obtained if these factors are not eliminated as far as possible.

A diet of low iodine content, but otherwise not rigorous, was recommended for one to two weeks prior to tracer tests and PBI analysis. This eliminated errors in PBI due to great variation in dietary intake of iodine—for example, fish foods, *et cetera*. In addition, perusal of some of the relevant literature (Riggs *et alii*, 1945; Wolff *et alii*, 1949; Childs *et alii*, 1950; Danowski *et alii*, 1950; Meyers *et alii*, 1951; Morgans, 1952) indicated that iodine or iodide, thiouracil derivatives, thyroid extracts and mercurial diuretics are all likely to influence the results of physical indices or PBI. Certain minimum periods of cessation of intake of such drugs were recommended rather empirically, as the exact time for which they can exert an effect is not known with certainty for a particular individual and varies to some extent with dosage levels and period of administration. Further investigation is necessary to determine the exact periods. The recommendations for the various preparations, to be followed wherever possible without prejudice to the clinical status of the patient, were as follows: (i) Thiouracil and its derivatives were to be withheld for a minimum period of two weeks prior to tracer studies with $I^{131}$ or analysis of PBI. When possible a period of four weeks is more satisfactory. (ii) Iodine and iodide or their derivatives, including cough mixtures *et cetera*, were to be withheld for four weeks (Wolff *et alii*, 1949; Childs *et alii*, 1950). (iii) Thyroid extracts or preparations were to be withheld for a minimum period of four weeks (Johnston *et alii*, 1951; Riggs *et alii*, 1945; Morgans *et alii*, 1952; Tritler, 1952). (iv) Mercurial diuretics ("Neptal", "Salyrgan" *et cetera*) were to be withheld for a minimum period of twenty-four hours prior to the collection of blood samples for PBI estimation, but not necessarily prior to the administration of tracer doses of $I^{131}$ (Meyers *et alii*, 1951). (v) A period of not less than two weeks was to elapse after intravenous pyelography in which iodine-containing radio-opaque substances were used. (vi) It is considered that analysis of PBI may give invalid results for several months after investigations in which "Lipiodol" is used or after cholecystography with certain iodine-containing preparations (Man and Peters, 1950).

### Details of Tests.

The original patients were admitted to hospital largely because collection of all urine excreted for seventy-two hours after a tracer dose of $I^{131}$ was necessary to estimate physical indices of excretion of $I^{131}$. Whilst they were in hospital, independent clinical appraisal of each patient was made by at least three physicians. It is notorious that clinical assessment of patients suffering from possible borderline thyrotoxicosis requires repeated observation over a period. This was not always possible if undue delay in proceeding with the tests was to be avoided. Hence ideal conditions for clinical diagnosis did not always exist. Whenever possible close follow-up examination, often including response to specific therapy, was undertaken in order to arrive at a definite final diagnosis. Clinical assessment and final diagnosis were always declared concurrently with the results of physical and biochemical investigations and were in no way influenced by the results of such tests. Whilst in hospital each patient had at least two independent estimations of basal metabolic rate, a tracer dose of $I^{131}$ and an analysis of PBI. At the same time any other routine clinical or laboratory investigations relevant to the case were carried out.

#### *Tracer Test Technique.*

In all cases $I^{131}$ (half-life eight days) was the isotope used. The $I^{131}$ was made available by the Commonwealth X-ray and Radium Laboratory in Melbourne, which conducted all the physical aspects of the project. The very early supplies of $I^{131}$ were obtained from the United States of America, but thereafter (1949) from the Atomic Energy Research Establishment, Harwell, England.

The intravenous route was used for all tracer doses in order to eliminate any possible errors of malabsorption from oral dosage. A "closed system" for intravenous injection was used to prevent any contamination or loss of the tracer dose. In the earlier studies, when measurements were carried out over several days, the tracer dose given was 100 microcuries of $I^{131}$ solution containing additional sodium iodide as carrier.

Each dose was dispensed at the Commonwealth X-ray and Radium Laboratory and supplied in a rubber-capped vial so that an accurate dose was available at the time of injection. The $I^{131}$ was sterilized by being boiled for twenty minutes in a domestic type pressure cooker to avoid any possible contamination of hospital equipment. A separate preparation room was available at the hospital and fitted with protective barriers and other necessary equipment for safe preparation and disposal of radio-active materials. Disposable sterile blotting paper was used in place of linen for all manœuvres associated with the injection of the $I^{131}$.

As the intravenous injection was given with the patient lying in position on a couch in the room containing the physical apparatus (Clarke and Aujard, 1953), alternate two-minute counts over the thyroid and thigh region, paired $\gamma$ counters being used, began immediately after the injection and were continued for thirty minutes.

Originally counting was carried out over the thyroid on successive days, and urinary samples were collected to determine excretion of $I^{131}$. When a sufficient number of tracer tests had been performed, a statistical analysis[1] of the results of physical indices and PBI estimation was made. This showed that the most accurate physically measurable index of thyroid function was related to uptake of $I^{131}$ in the thyroid gland (Clarke and Aujard, 1954). The PBI estimation was shown to be even more accurate than physical measurements of $I^{131}$ tracer doses by this analysis. Thereafter it was decided that the use of

[1] The statistical analysis was made by Dr. F. E. Binet, Department of Statistics, University of Melbourne.

excretion indices should be discontinued. By this time a sufficient number of patients had had their basal metabolic rate calculated to show that it was an inaccurate index of thyroid function, and the test was no longer included. It was now possible to investigate patients as out-patients and to reduce the quantity of $I^{131}$ to 20 microcuries (carrier free) for each tracer dose.

Goodwin, MacGregor, Miller and Wayne (1951) showed that calculation of protein-bound radio-active iodine in blood forty-eight hours after the tracer dose of $I^{131}$ was a most useful addition to tracer studies, and this index was therefore included. A further additional index discussed in a later paper (U25-U15) was substituted in place of excretion indices. Therefore, the procedure in its more simplified form makes it unnecessary to admit a patient to hospital. It is convenient to enumerate the various important stages as follows: (i) Each patient attends for clinical assessment by independent medical observers. (ii) A special diet of low iodine content is recommended for one to two weeks. (iii) Tracer studies with $I^{131}$ and analysis of PBI are delayed for the appropriate period if the subject has been taking substances likely to influence these tests. (iv) A tracer dose of 20 microcuries of $I^{131}$ carrier-free is given intravenously by means of a closed system. (v) Alternate two-minute counts over the thyroid and thigh by the use of paired $\gamma$ counters begin immediately after injection and are continued for thirty minutes. (vi) Just prior to the tracer dose a sample of venous blood is obtained for estimation of PBI. (vii) The patient returns for a short visit forty-eight hours later, when a further sample of venous blood is obtained for estimation of PBI and $PBI^{131}$. (viii) Further frequent clinical assessment of each patient is made whenever the functional status of the thyroid is equivocal.

## Analysis of Results of Tracer Tests with $I^{131}$ and PBI Estimations.

The results of 140 tests on 114 patients are available for analysis. Reasons have already been given for omitting 12 tests and for not including tests performed on normal controls. The criterion on which the result of any test was judged was the agreed final diagnosis. Therefore, in the event of clinical assessment of thyroid function at the time of the test being subsequently shown to be incorrect, an apparently incorrect physical index may in retrospect be shown to be correct. Such alterations of original clinical assessment are unavoidable whenever a large number of patients with known or suspected thyroid disorders and sometimes associated medical diseases are seen. If this was not so, then investigations and laboratory tests would be unnecessary. Consequently, unless thyroid dysfunction was clinically obvious, it was often necessary to review a particular patient on several occasions or to await response to medical treatment before deciding whether symptoms and signs were in fact due to disorder of the thyroid gland. At the same time it was necessary as part of the project to have a clinical assessment at the time of the test. It must be stressed that in arriving at a final diagnosis, clinical progress alone was considered and no cognizance was taken of the results of tracer tests or PBI values in influencing a decision in equivocal cases. Of course, when the reliability of such tests is established it is only sensible that they should be considered as important factors in deciding the diagnosis in an uncertain case. With the usefulness of the tests under examination as part of a project, this could not be permitted.

The patients considered in this analysis are divisible on the basis of final diagnosis into the three ordinarily accepted states of thyroid function: (i) non-toxic (euthyroid)—Group I; (ii) toxic (hyperthyroid)—Group II; (iii) hypothyroid (myxœdema or cretinism)—Group III. Each group is conveniently discussed separately.

### Group I: Final Diagnosis Non-Toxic Goitre.

Group I consisted of 66 patients who had a total of 72 tracer tests with $I^{131}$. Tests were repeated as necessary when there was alteration in the clinical condition of the patient, or when "influencing medication" had been discontinued for only a short period. In addition there were examples in this group of patients who, although originally thyrotoxic, had lost their thyrotoxicosis with treatment.

Each patient was investigated because of signs or symptoms that could be due to thyroid dysfunction. The types of clinical problems seen can be appreciated by classifying the patients into broad clinical varieties. The final diagnosis in the 66 cases concerned varied as follows: (i) "neurasthenia", with or without a coexistent non-toxic thyroid enlargement, 12 cases; (ii) non-toxic diffuse goitre, 21 cases; (iii) non-toxic nodular goitre, 10 cases; (iv) cardiac disorders of various ætiology—for example, hypertension, vascular disease, neuro-circulatory asthenia—some with coexistent goitre; auricular fibrillation was present in seven of a total of 10 cases in this class; (v) hyperthyroidism arrested or in remission, eight cases; (vi) pituitary disorders (acromegaly, *et cetera*), four cases; (vii) progressive muscular atrophy, one case. This broad subdivision gives some idea of the type of patients examined and hints at the clinical problem of diagnosis for many of them.

In analysing the usefulness of tracer studies with $I^{131}$ and estimations of PBI and basal metabolic rate, compared with clinical assessment, each factor is best discussed independently.

#### *Clinical Assessment.*

Although conditions were not always ideal, particularly for out-patients, every attempt was made to discover the medical and social background of each subject, to eliminate unnecessary stress, to include any relevant routine clinical investigations and to carry out a complete medical examination by each observer. Whenever doubt existed about thyroid function, further interviews were arranged. In four cases the original clinical assessment had to be considered incorrect after repeated clinical appraisal. It is obvious that no physician can hope to deal with a large number of patients suspected of thyroid disorder without changing his first opinion for some patients. However, it is still true that no test or investigation is as yet available which can replace careful clinical methods for arriving at a diagnosis.

#### *Physical Indices.*

From 1950 until 1952 the physical index used to determine thyroid function was $k_1$ (Clarke and Aujard, 1954). Since then the index U25-U15 has been used. With a few exceptions $k_2$ has not been evaluated in the second series of patients. In choosing the range of values for these indices to separate normal, hyperthyroid and hypothyroid subjects, cognizance was taken of the results on normal controls and some of the preliminary patients with obvious dysfunction tested prior to 1950.

Of the 72 tests performed on 66 patients eventually diagnosed as having normal thyroid function, 61 tests gave correct classification by the physical indices and were in agreement with the final estimation of thyroid function. Consequently there were nine tests, with no influencing medication known to invalidate the results, which misclassified the patient's status. An additional two tests gave values for physical indices which were "uncertain". It has not been possible to choose particular values for these physical indices that will categorically separate all patients into distinct groups—that is, normal, hypothyroid or hyperthyroid states. There is a slight overlap in the value of the physical index between groups—for example, the highest acceptable as "normal" and the lowest acceptable as "hyperthyroid".

Uncertain values, particularly when a tracer test was repeated on a patient, sometimes suggested a trend towards a particular grouping—for example, "more likely normal than toxic"—but in this an analysis is notwithstanding considered to be incorrect.

*PBI Estimations.*

The normal "non-toxic" range for PBI was considered to be between 3·0 and 7·5 microgrammes per 100 cubic centimetres of blood plasma. Values from 7·5 to 8·0 microgrammes were regarded as "borderline", as were values from 2·7 to 3·0 microgrammes. Two separate estimations of PBI were made for each patient.

PBI was analysed in association with 67 tests in this group. It had to be omitted from five tests because of contamination of specimens. The results gave an incorrect assessment of thyroid function in two tests, and were "borderline" for four tests. Here again a borderline result was considered erroneous. Therefore, PBI estimation gave a correct assessment of thyroid function in a total of 61 tests out of the 67 performed.

*Basal Metabolic Rate Estimation.*

After a statistical analysis, the basal metabolic rate was found to be an unreliable index of thyroid function, so that it was omitted from later tests. It was included in 47 tests. The "normal" range for the particular method employed was ±10%. On this basis wrong or uncertain values were obtained for the basal metabolic rate in 22 tests of the 47 carried out.

**Group II: Final Diagnosis Hyperthyroidism (Toxic).**

In Group II 65 tracer tests were performed on 45 patients. The patients showed varying manifestations of hyperthyroidism, which are conveniently subdivisible into the following major types: (i) primary or recurrent thyrotoxicosis with severe exophthalmos, 18 patients; (ii) primary thyrotoxicosis without exophthalmos, 16 patients; (iii) thyrotoxicosis with predominant cardiac symptoms, nine patients; (iv) retrosternal toxic goitre, one patient; (v) thyrotoxicosis and pre-tibial myxœdema, one patient.

The severity of the toxicity was variable. Some patients were obviously hyperthyroid and primarily examined for consideration of $I^{131}$ therapy. Twenty-three of the 45 in the group were treated with $I^{131}$ and are discussed later. Other patients were not obviously in a toxic condition and were investigated as presenting diagnostic problems. Typical examples were patients with cardiac disease of variable ætiology who were investigated for a possible thyrotoxic element, or patients who had already had surgical treatment for thyrotoxicosis and had symptoms suggesting recurrence. Most of the classical signs, symptoms and modes of onset of the disease were noted, with the exception that no example of thyrotoxic myopathy was encountered. Tracer tests had to be repeated on particular subjects for one or more of the following reasons: (i) to eliminate possible error from influencing medication; (ii) to assess response to therapy with $I^{131}$; (iii) as a preliminary to repeated therapy doses of $I^{131}$; (iv) to investigate alteration in $I^{131}$ metabolism at a particular period after cessation of medication with thiouracil or iodine.

An analysis of this group of patients gave the following results for the various investigations undertaken.

*Clinical Assessment.*

The preliminary assessment of thyroid function required revision after repeated clinical examinations for eight of the total of 65 patients. In arriving at a final diagnosis the results of tracer tests or PBI estimations were not allowed to influence clinical diagnosis. It is in relation to such patients that these tests, once established as being accurate indicators of thyroid function, can help in arriving more quickly at a diagnosis in cases of doubt. Whilst the tests were being investigated this was not permissible.

*Physical Indices.*

In all, nine hyperthyroid patients with no influencing medication were misclassified according to physical indices, and one additional patient gave borderline or uncertain values. In addition three hyperthyroid patients with influencing medication were misclassified. Therefore, it would appear that the physical index is likely to give an accurate assessment of thyroid function in four-fifths of cases.

*PBI Estimation.*

The PBI was estimated in association with 61 tests—omission occurring, for example, when a tracer test was performed as a preliminary to a repeated therapy dose of $I^{131}$. Additional PBI estimations were made independently of tracer tests for follow-up investigation of patients being treated with $I^{131}$. These are not included in this analysis. There were known influences of medication likely to affect PBI in two tests, and in each case a wrong assessment of thyroid function was obtained. There were borderline results for eight tests on six separate patients. There were two tests on two separate patients without any known influencing medication which gave wrong assessment of thyroid function. Hence the PBI was in agreement with the final diagnosis in association with 49 tests of a total of 59.

*Basal Metabolic Rate.*

Basal metabolic rate estimation was included in 28 tests and gave erroneous or inconclusive assessment of the functional state of the thyroid in 13 tests.

**Group III: Final Diagnosis Hypothyroidism.**

The physical indices investigated were those which were expected to distinguish between normal and hyperthyroid subjects; for this purpose other indices not investigated may prove more suitable. For this reason only three cases of proven hypothyroidism were fully investigated, and with so few it is not reasonable to draw any real conclusion. However, in several cases of known or suspected hypothyroidism a PBI analysis was carried out, and these are discussed in a later paper.

The three cases investigated fully comprised a case of juvenile myxœdema, a case of cretinism and a case of Hashimoto's thyroiditis.

Clinical assessment did not require revision for any patient. Physical indices, although calculated, were considered unsuitable for differentiation between normal and hypothyroid function. A correct value indicating hypothyroidism was obtained for PBI for the patient with cretinism, an uncertain value for the patient with Hashimoto's disease, and a "toxic" level of PBI with estimations repeated on many occasions over a long period in the third case. The possibility of unusual tissue tolerance to circulating hormone arose. The basal metabolic rate gave correct assessment in two of the three patients.

The results of the analysis of each group are summarized in Table I.

**Summary of Over-all Results.**

1. Clinical assessment gave correct classification for 128 of the total of 140 tests.

2. Physical indices gave correct classification for 113 tests, inconclusive for six tests and incorrect for 21 tests of the total of 140 performed.

3. PBI estimation gave correct classification for 111 tests, inconclusive results for 13 tests and incorrect results for seven tests of a total of 131 performed.

4. The basal metabolic rate gave correct classification for 40 tests and inconclusive or incorrect results for 36 of the total of 76 performed.

**Discussion.**

Investigations on large numbers of subjects reported by such authors as Keating *et alii* (1947), Werner *et alii* (1948), Skanse (1949), Myant *et alii* (1949), and Jaffé and Ottoman (1950) have already produced evidence of the merits of various physical indices calculated from tracer doses of $I^{131}$ and of their value in aiding the diagnosis of thyroid disorders. This present analysis, in which $k_1$ and U25-U15 were the particular indices investigated, indicates that the initial rate of uptake of $I^{131}$ by the thyroid gland offers a reliable and quickly obtainable physical measure-

TABLE I.

*Summary of Results of Tracer Tests.*[1]

(i) Prior to 1950, 65 tests on 56 patients.

(ii) 1950 to 1953: Total number of tests, 184 tests on 148 patients, as follows: (*a*) 72 tests on 66 patients in non-toxic state; (*b*) 65 tests on 45 patients in toxic state; (*c*) three tests on three hypothyroid patients; (*d*) 32 tests on 32 normal control patients; (*e*) 12 tests on 11 patients omitted, nine of these patients being included elsewhere.

| Thyroid Status Final Diagnosis. | Clinical Assessment Revised. | Physical Indices. | | | Protein-Bound Iodine. | | | Basal Metabolic Rate. | |
|---|---|---|---|---|---|---|---|---|---|
| | | Correct. | Inconclusive. | Incorrect. | Correct. | Inconclusive. | Incorrect. | Correct. | Incorrect. |
| Group I: "Non-Toxic"—72 tests on 66 patients .. | 4 tests. | 61 tests. | 2 tests. | 9 tests. | 61 tests. | 4 tests. | 2 tests. | 25 | 22 |
| Group II: "Toxic"—65 tests on 45 patients .. | 8 tests. | 52 tests. | 1 test. | 12 tests. | 49 tests. | 8 tests. | 2 tests. | 15 | 13 |
| Group III: "Hypothyroid"—3 tests on 3 patients .. | 0 | 0 | 3 tests. | 0 | 1 test. | 1 test. | 1 test. | 2 | 1 |

ment of the thyroid function, which aids in the diagnosis of suspected hyperthyroidism and usefully separates hyperfunction from normal function in the majority of subjects investigated. Whenever masked thyrotoxicosis, thyrocardiac disease or simple goitre is suspected of causing hyperthyroidism, tracer studies with $I^{131}$ can be of great aid to the physician in arriving at the correct diagnosis. The index $PBI^{131}$ at forty-eight hours is still being investigated, but promises to be useful in diagnosis. The difficulty still remains that a particular value of a physical index ($k_1$, U25-U15, $PBI^{131}$ at forty-eight hours) may be borderline, as it is not possible to have a clear separation between the highest value indicating normal thyroid function and the lowest value found with hyperthyroidism. At the moment this borderline zone is arbitrarily set, but it may be possible to narrow it with further experience. In addition it may be possible to take more than one index into consideration (for example, U25-U-15 and $PBI^{131}$ at forty-eight hours) when a borderline value is obtained for a particular patient. The present feeling is that it is sounder to set the limits for physical indices so that a patient in a mildly toxic state is misclassified, rather than to misclassify a patient in a truly non-toxic state as being hyperthyroid. It is considered that a "missed toxic" patient will probably reveal his true functional thyroid status after repeated clinical observation; at the same time a patient in a truly non-toxic state will not be subjected to unnecessary therapy.

Our experiences with tracer studies with $I^{131}$ for patients with myxœdema does not permit any conclusions, but it is believed that with the physical indices being used by us at present no reliable separation of normal from mildly hypothyroid function can be made. Tracer studies with $I^{131}$ can now be carried out in any properly equipped hospital with little or no inconvenience to an attending outpatient, and provided the necessary recommendations concerning medication are followed. With a reliable physical index such as U25-U15, the result of the test is available very soon after its completion. With the dosage and technique used there should be no radiation hazards for patient or staff. Once established, apart from the original cost of apparatus, the test is relatively inexpensive. It is considered that the use of the intravenous route for the $I^{131}$ adds to the accuracy of the test with no real additional discomfort for the patient. Once the value of the physical test is established, it is permissible to place as much significance on a particular result as with other clinical tests of similar accuracy, and certainly more significance than on the basal metabolic rate estimation.

Estimation of PBI in plasma gives a direct indication of the level of circulating thyroid hormone, even though it is not a measurement of the actual hormone.

Although the basic ætiology of hyperthyroidism is still undecided, the level of thyroid hormone in the blood is a mirror of thyroid functional status, so that PBI gives direct evidence of the activity of the gland. A statistical analysis of the results of earlier tests showed PBI to be more accurate as an index of thyroid function than the physical indices considered. The overall results of PBI analysis are to be found in Table I. As with the physical indices, there is no sharp demarcation between the highest normal and the lowest toxic PBI figure. From the patient's viewpoint PBI analysis simply involves obtaining a specimen of venous blood. It is much more useful for cases of suspected hypothyroidism than physical indices investigated by us. Again, there is a borderline zone of values of lowest normal and highest hypothyroid. One disadvantage is the elaborate laboratory technique needed and the overall expense, so that PBI estimation can be made only in a properly established biochemistry department with suitably trained personnel.

Most clinicians agree that estimation of the basal metabolic rate by the standard technique can give very variable results in a group of patients with thyroid dysfunction, and that in a clinically equivocal case it is not of much aid. Conditions of hyperventilation, nervousness, tremors or cardiac failure which are often present in association with thyrotoxicosis are of themselves liable to cause an elevated basal metabolic rate. In addition, a raised level is to be expected with hypermetabolic states other than thyrotoxicosis (Kyle, 1950). The statistical analysis of the earlier tests showed it to be an unreliable test for thyroid function, and it was thereafter abandoned.

The following is a report of a typical case in which tracer studies and PBI estimation are useful:

CASE 5.—A female patient, aged forty-two years, had undergone subtotal thyroidectomy in 1935 for frank thyrotoxicosis. She developed palpitations, headaches and nervousness in 1946, which were considered to be due to essential hypertension. In 1952, three months prior to investigation, she noted tremor of the hands, profuse sweating, irritability and nervousness and slight loss of weight. The basal metabolic rate at that time was +100%. When she was examined three months later the patient was thin and nervous with fine tremor of her hands, slight lid lag and sweating. The thyroid was not palpable. Her pulse rate was 110 per minute and regular. Her blood pressure was 220 millimetres of mercury, systolic, and 120 millimetres, diastolic. There was slight left ventricular enlargement and a grade III systolic murmur at the apex. She was clinically considered to be suffering from essential hypertension and recurrent thyrotoxicosis. Tracer studies with $I^{131}$ gave "non-toxic" results. The PBI figure was normal (5·1 microcuries per 100 cubic centimetres of blood). Further repeated observation after rest in bed and response to therapy showed that all her symptoms were due to essential hypertension.

If the results of tracer studies and PBI estimations had been taken on their face value, they would have given a correct diagnosis prior to repeated clinical observation.

### TREATMENT OF THYROTOXICOSIS WITH $I^{131}$.

For at least thirty years and particularly before the advent of thiouracil derivatives, external irradiation has been a recognized alternative to surgical treatment and iodine therapy in cases of thyrotoxicosis. The biological effects of such irradiation tend to decrease the functional

activity of the relatively radio-sensitive over-active toxic gland (Larsson and Ragnhult, 1953), and to reduce the output of thyroid hormone. In general this method of treatment was always confined to patients not desiring or considered unsuitable for surgical or medical treatment. However, many radiotherapists have seen remarkable benefit in some patients.

It is almost thirty years also since Marine showed that the normal thyroid has a unique capacity to concentrate iodine to a level 10,000 times that of the blood. Therefore, when radio-active iodine ($I^{130}$ and $I^{131}$) became available as non-toxic sources of $\beta$ and $\gamma$ radiation, the possibility of rather localized internal irradiation of a hyperfunctioning thyroid gland was widely appreciated. The isotope $I^{131}$ became the one of choice because of its more suitable half-life of eight days, compared with that of $I^{130}$ (0·42 hour).

In the last five years there have been numerous reports in the literature of the results of treating large numbers of patients with this drug (Marinelli, Quimby and Hine, 1948; McCullagh and Richards, 1951; Portman *et alii*, 1951; Scott *et alii*, 1951; Crile and McCullagh, 1951; Blomfield *et alii*, 1951). The experience with $I^{131}$ therapy of this group, although limited to a small number of patients, may add some contribution to the rapidly increasing experience with $I^{131}$ as a therapeutic agent.

As yet there is no final agreement as to what are the absolute indications and contraindications for using $I^{131}$ as the sole therapeutic agent in hyperthyroidism. Recently Seed and Jaffé (1953) and Wohl *et alii* (1953) have given more specific indications of dosage levels to be employed and of the types of cases best suited for $I^{131}$ therapy. It was the policy of this group during the investigation largely to confine the use of this isotope to patients for whom surgical removal of the gland or medication with anti-thyroid drugs had either failed to control the disease or was contraindicated for other reasons. In addition the medical management of many of the patients referred for investigation was often decided by the doctor referring the patient.

The chief objection to $I^{131}$ therapy for hyperthyroidism has been the possible danger of radiation hazards to the patient. Development of late malignant change and genetic effects are the two chief concerns. By now many centres in which $I^{131}$ has been administered to large numbers of patients are placing less and less emphasis on these fears; but it still remains an undetermined question. The vast accumulated evidence for almost fifty years of irradiating with X rays and naturally occurring radio-active materials the chief areas of the body concerned with the metabolism of an administered dose of $I^{131}$—thyroid gland, kidneys, bladder and liver—suggests that the dangers of producing malignant change with therapy doses of $I^{131}$ have been overstressed if one is permitted to draw a parallel. It is, moreover, considered that production of genetic mutations in the gonads of patients given $I^{131}$ therapy for thyrotoxicosis is unlikely. This conclusion is based on an estimation of the maximum dosage likely to be received by the gonads in the female under the most adverse circumstances from a therapy dose of $I^{131}$ given for thyrotoxicosis. In a patient who fails to empty her bladder normally and in whom the gonads are within the closest proximity to the bladder, physical calculations suggest that there is often a greater dosage in *r* delivered to the gonads by radiographic procedures such as pelvimetry than is likely with doses of the order of 10 millicuries of $I^{131}$ (Clarke, 1953). Ritter, Warren and Pendergrass (1952) have shown the type of dosage in *r* delivered to various anatomical sites in association with certain common radiographic procedures. With these ideas in mind, it is not considered reasonable to withhold tracer doses of the order of 20 microcuries of $I^{131}$ from patients when tracer studies with $I^{131}$ are considered to offer diagnostic aid. Until more information is available, it may be preferable not to use radio-active iodine as the first line of treatment for patients with thyrotoxicosis younger than thirty-five years, except when other methods of treatment have failed or are contraindicated. On this basis the type of cases in which $I^{131}$ was used in this series consisted of the following chief groups: (i) recurrent thyrotoxicosis after surgery or medical treatment; (ii) uncontrolled thyrotoxicosis after a reasonable trial with antithyroid drugs; (iii) thyrotoxicosis with progressive exophthalmos; (iv) thyrotoxicosis with maximal cardiac incidence; (v) special unusual circumstances such as mental disorders, lack of alternative measures of treatment and unreliability in taking medication.

The one unequivocal contraindication to $I^{131}$ therapy is probably in a patient more than fourteen weeks pregnant because of the danger of damage to the developing fœtal thyroid. Chapman, Corner, Robinson and Evans (1948) have studied the collection of radio-iodine by the human fœtal thyroid, and suggest that a pregnant female can be safely treated with $I^{131}$ up to the fourth month of pregnancy.

Until recent years it has been considered by pathologists that a nodular goitre was more prone to subsequent malignant change than the diffuse variety. Although this belief has been challenged by people with wide experience, it is an unresolved question. Moreover, because of their proneness to large size and varying complications, such as tracheal obstruction and internal hæmorrhage, a nodular toxic goitre is still probably best treated by surgical extirpation. Moreover, the "spotty" uptake of a therapeutic dose of $I^{131}$ is less likely to cause a clinical remission of hyperthyroidism and reduction in gland mass. Above all, the results of treating large toxic nodular goitres with $I^{131}$ in other clinics show a significant proportion of failures. With these ideas in mind, the presence of a large nodular toxic goitre is possibly a contra-indication to $I^{131}$ therapy except when an alternative method of treatment is contraindicated for other reasons—for example, refusal of surgical treatment, intolerance to thiourylene derivatives. The general policy at the moment is to advise surgery as the main line of treatment for such glands.

### Dosage Considerations.

As with all forms of radiotherapy, there is a choice between single large doses of radiation and fractionated smaller doses. In general, the use of fractionated small doses is now established as the more reliable and safe method of irradiation with X and $\gamma$ rays. In the early cases of thyrotoxicosis treated from 1949 to 1951 it was decided to fractionate dosage in an endeavour to avoid myxœdema or thyroid crisis. The latter was probably grossly overstressed in our minds because of the onset of a thyroid crisis in a patient with well-differentiated metastatic carcinoma of the thyroid (reported below) after $I^{131}$ therapy. The original policy was to administer a dose of 5000 equivalent röntgens (hereinafter called e.r[1]). This was soon after increased to 6000 e.r. For the calculation of dosage it was necessary to determine the uptake and retention of a tracer dose of $I^{131}$ and to estimate the mass of the thyroid gland. Estimation of the mass of the thyroid was attempted by outlining its contours when palpable, reconstructing a volumetric diagram and so estimating total volume. The specific gravity of the tissue was arbitrarily taken as being unity. Such a procedure is, of course, subject to gross error and can at best be but an approximation. The only possible advantage was that these estimations of size were always made by the same personnel.

Consideration of the patients treated shows that this method and level of dosage have not been sufficiently accurate to control the condition in some of them. However, they have proved a useful foundation on which to base present dosage recommendations. In the treatment of patients receiving medication who are in a severely toxic state, particularly in the presence of mental symptoms, it is not always possible to plan dosage in connexion with a preliminary tracer test. Such cases, of necessity, demand empirical dosage and adjuvant treatment with thiourylene drugs as soon as sufficient time has elapsed for significant uptake of a therapy dose of $I^{131}$.

[1] The equivalent röntgen is defined as "that amount of beta radiation which under equilibrium conditions releases in one grain of air as much energy as one röntgen of gamma rays".

*Mode of Administration of Therapy Doses of $I^{131}$.*

The original patients treated—thyrotoxic and with malignant disease—were given intravenous therapy. This method was soon abandoned in favour of the oral route, as only a minute percentage of the administered dose is lost through malabsorption in the alimentary tract. Gastric biopsies performed on a few patients given oral therapy failed to reveal any untoward pathological changes. It was also considered that there was less likelihood of contamination of personnel and materials than with intravenous therapy.

The dose was presented to the patient in a glass container enclosed within a lead-lined box, and imbibed with a glass drinking straw. Out-patients were given directions concerning disposal of excreta, and in-patients had specially labelled urinals and bed-pans for their exclusive use. General recommendations laid down regarding disposal of radio-active waste were adhered to.

Each patient was reviewed when possible one week after the therapy dose to inquire about any untoward effects. No example of thyroiditis was noted. An interval of three months was considered to be the total time during which biological changes in the thyroid were likely to occur after a therapy dose. Full clinical assessment and estimation of PBI were carried out at monthly intervals. When control of toxicity was not apparent after three months, a further tracer test was made and a repeated therapy dose was given. The dose had to be repeated for a third time after a further three months in some cases. This is, however, considered undesirable, and if the original dose is inadequate there may be some resistance thereafter, much larger subsequent doses being required.

**Adjuvant Management.**

Certain features of thyrotoxicosis when treated with radio-active iodine are likely to demand adjuvant therapeutic measures. These are mainly the following: (i) severe toxicity, (ii) progressive exophthalmos, (iii) myxœdema, (iv) pre-tibial myxœdema.

In the treatment of a patient in a severely toxic state, it may not be safe to withhold other drugs until a therapy dose of $I^{131}$ begins to control the hyperfunction of the thyroid gland. A period of from four to twelve weeks is to be expected before improvement is noticed. It is during this interim that thiouracil derivatives can be usefully employed, provided that such medication is withheld without danger to the patient for a sufficient period after a therapy dose to permit maximal utilization of the $I^{131}$. In practice a period of five days is a usual time after which thiouracil therapy may be commenced. These drugs can be discontinued when the $I^{131}$ therapy begins to have effect. An endeavour has been made to investigate the practicability of using $I^{131}$ therapy for patients who are already receiving "thio" drugs, and who are clinically considered to require a minimal period of cessation of their administration. This investigation is proceeding. Tracer studies with $I^{131}$ have been carried out on some patients to investigate this matter; but sufficient evidence is not yet available to determine the minimum practical period for temporary cessation of administration of "thio" drugs to obtain significant uptake of a therapy dose of $I^{131}$.

Progressive exophthalmos remains one of the most serious and least responsive to treatment of the many manifestations of thyrotoxicosis. With the known danger of aggravating the condition by surgery and the unpredictable response to thiourylene drugs, even when combined with stilbœstrol and thyroid, the addition of $I^{131}$ to the therapeutic armamentarium offered an alternative method of treatment. A possible theoretical advantage was that $I^{131}$ permits a gradual "subtotal thyroidectomy" favouring thyroid-pituitary balance. In this series there were nine cases of severe progressive exophthalmos treated with $I^{131}$. Irradiation of the pituitary with X rays was added in six cases—a tumour dose of 3000*r* in four weeks. Encouraging results from irradiating the post-orbital tissues for exophthalmos were reported by Jones (1951). In the four cases in the present series in which this method of treatment was used, there was no obvious benefit.

There are now many reports in the literature of transitory or established myxœdema as a sequel to radio-iodine therapy. The general incidence in large series of cases is in the order of 6% to 10%. There was one example of mild myxœdema arising after $I^{131}$ therapy in the 23 cases here reported. However, it will be seen later that the error in these cases was towards underdosage rather than overdosage. As far as can be seen from other workers, there is no special difficulty in the management of post-irradiational myxœdema, and it would appear unlikely that any method of dosage which is adequate to control hyperthyroidism will guarantee freedom of all patients from hypothyroidism.

An unusual association with thyrotoxicosis is pre-tibial myxœdema. A recent report by Grynkewich, Laughlin, Herron and Carmel (1951) stressed the rarity of coincidental thyrotoxicosis with exophthalmos and pre-tibial myxœdema. There was one such case in this series. Therapy with $I^{131}$ did not have any good or bad effect on this particular symptom. Adjuvant treatment given included stilbœstrol, thyroid extract and local instillation of hyaluronidase without improvement, although toxicity was controlled by $I^{131}$.

**Analysis of Patients with Hyperthyroidism Treated with $I^{131}$.**

A total of 23 patients with thyrotoxicosis were treated with $I^{131}$. These included the following clinical subgroups: (i) severe thyrotoxicosis with progressive exophthalmos, four patients; (ii) thyrotoxicosis recurrent after surgical treatment: (*a*) with severe exophthalmos, two patients; (*b*) with exophthalmos and pre-tibial myxœdema, one patient; (*c*) without exophthalmos, four patients; (iii) thyrotoxicosis with predominant cardiac incidence: (*a*) with exophthalmos, two patients; (*b*) without exophthalmos, five patients; (iv) primary thyrotoxicosis, surgical treatment refused, four patients; (v) thyrotoxicosis with mental changes and exophthalmos, one patient. These cases are briefly reported below.

Of the 23 patients treated, three have since died of cardiac failure existent at the time of $I^{131}$ therapy and of hypertensive or rheumatic ætiology in addition to a thyrotoxic element. Two of these patients had their thyrotoxicosis controlled by a single dose of $I^{131}$, and the other died two months after a single therapy dose with only partial control, if any.

Twenty patients are still alive and being reviewed at frequent intervals. The total number of therapy doses given varied from one to five, as follows: (i) single dose, eight patients and three patients who have died from other causes; (ii) two doses, five patients; (iii) three doses, five patients; (iv) four doses, two patients.

Ten patients (*Cases 20, 21, 28, 56, 57, 58, 63, 67, 87, 116*) had their condition controlled and have been under observation since the last therapy dose for periods varying from six months to three years. This was achieved by a single dose for six patients, by two doses for two patients, and by three doses for two other patients. Of the remaining ten patients, four have their condition improved but only partly controlled. In these four cases the period of observation since the last dose has been between two and six months. Two of these patients have had a single dose of $I^{131}$, another patient has had three doses and the remaining patient has had four doses.

There remain five patients who have been in a non-toxic state since their last therapy dose was given three to five months ago, so that insufficient time has elapsed up to the present to determine whether their condition will be controlled. Two of these have already had two therapy doses, another two have each had three therapy doses, and the remaining patient has had four therapy doses (see Table II).

TABLE II.

*Table of Results of $I^{131}$ Therapy.*

| Case Number. | Clinical Type. | Indications for $I^{131}$. | Number of Doses. | Doses in Millicuries. | Response. | Final Result. | Interval Since Last Dose. |
|---|---|---|---|---|---|---|---|
| 9 | Primary thyrotoxicosis. | Progressive exophthalmos; cardiac failure. | 3 | 2·1<br>3·2<br>2·3 | Improved.<br>Improved.<br>Improved. | Non-toxic. | 4 months. |
| 11 | Primary thyrotoxicosis. | Refused operation; large goitre made use of thiouracil unwise. | 2 | 5·38<br>6·0 | Much improved. | Non-toxic. | 4 months; mildly hypothyroid. |
| 12 | Nodular toxic goitre. | Severe toxicity; no control by thiouracil; exophthalmos and ophthalmoplegia. | 2 | 4·0<br>4·0 | Improved.<br>Improved. | Reverted to thiouracil, and condition controlled. | 2 years. |
| 16 | Retrosternal toxic goitre (thyrocardiac). | Retrosternal goitre; thyrocardiac disease. | 2 | 2·6<br>2·5 | Non-toxic for three months.<br>Non-toxic. | Non-toxic. | 5 months. |
| 20 | Nodular toxic goitre recurrent after operation. | Recurrence after operation; large goitre. | 1 | 8·0 | Non-toxic. | Non-toxic; still has ischæmic heart disease. | 2 years. |
| 21 | Recurrent thyrotoxicosis after operation. | Recurrence after operation; incomplete control with thiouracil. | 1 | 1·7 | Non-toxic. | Non-toxic. | 18 months. |
| 25 | "Secondary" toxic goitre with exophthalmos. | Lack of response to medical treatment; acute mania. | 3 | 3·0<br>4·7<br>4·0 | Greatly improved.<br>Improved.<br>Improved. | Non-toxic. | 3 months. |
| 28 | Primary thyrotoxicosis. | Physician advised $I^{131}$. | 1 | 5·0 | Improved. | Non-toxic. | 18 months. |
| 44 | "Masked" thyrocardiac. | Failure to respond to cardiac treatment. | 1 | 1·0 | Improved. | Non-toxic. | Died 9 months later from hypertension. |
| 52 | Thyrocardiac with exophthalmos. | Severe toxicity, age, thyrocardiac condition, exophthalmos. | 3 | 7·0<br>9·2<br>7·0 | Greatly improved.<br>Improved.<br>Improved. | Mildly toxic. | 4 months. |
| 56 | "Secondary" toxic goitre. | Opposed to surgery. | 1 | 6·0 | Improved; non-toxic. | Non-toxic. | 6 months. |
| 57 | Primary thyrotoxicosis. | Opposed to surgery; poor control with thiouracil. | 1 | 6·0 | Improved. | Non-toxic. | 6 months. |
| 58 | Primary thyrotoxicosis; "malignant" exophthalmos. | Poor response to thiouracil; severe toxicity; severe exophthalmos. | 2 | 6·0<br>6·0 | Improved.<br>Non-toxic. | Non-toxic. | 2 years. |
| 60 | Recurrent thyrotoxicosis after operation. | Recurrence after operation; thyrocardiac disease; exophthalmos. | 1 | 5·0 | Improved. | Still toxic. | 6 months. |
| 62 | Recurrent nodular toxic goitre after operation. | Recurrence after surgery; exophthalmos. | 4 | 2·0<br>2·3<br>5·0<br>3·0 | Improved.<br>Improved.<br>Improved.<br>Improved. | Partly controlled. | 2 months. |
| 63 | Primary thyrotoxicosis; exophthalmos; ophthalmoplegia. | Severe exophthalmos. | 3 | 6·0<br>4·8<br>6·0 | Non-toxic.<br>Improved. | Non-toxic. | 18 months. |
| 67 | Primary thyrotoxicosis; exophthalmos. | Exophthalmos. | 2 | 2·0<br>1·7 | Improved.<br>Improved. | Non-toxic. | 18 months. |
| 75 | Primary thyrotoxicosis. | Advised by her physician. | 1 | 6·2 | Non-toxic. | Mildly toxic. | 5 months. |
| 80 | Recurrent thyrotoxicosis after operation. | Recurrence after operation; poor control with thiouracil. | 4 | 3·5<br>1·5<br>1·0<br>2·0 | Improved.<br>Improved.<br>Improved.<br>Improved. | Mildly toxic. | 2 months. |
| 87 | Recurrent thyrotoxicosis after operation, with exophthalmos. | Recurrence after operation; pre-tibial myxœdema; exophthalmos. | 3 | 1·0<br>4·0<br>3·0 | Improved.<br>Improved.<br>Improved. | Non-toxic. | 8 months. |
| 100 | Thyrocardiac disease. | Thyrocardiac disease. | 1 | 2·1 | Non-toxic. | Non-toxic. | Died 8 months after dose. |
| 116 | Recurrent thyrotoxicosis after radiotherapy. | Operation prevented by skin damage; intolerant to thiouracil. | 1 | 3·2 | Non-toxic. | Non-toxic. | 3 years. |
| 117 | Thyrocardiac element in association with rheumatic heart disease. | Uncontrolled congestive cardiac failure. | 1 | 3·7 | Not improved. | Died. | Died 2 months after therapy dose. |

It is apparent from these results that the original method of assessing dosage has not been satisfactory, at any rate when 5000 to 6000 *r* are given. Whenever more than two therapy doses are necessary, it is considered that inadequate control is being obtained, and the time interval associated with the need for three or more doses to control thyrotoxicosis makes such therapy less satisfactory than surgical treatment. This, however, is a criticism not of the efficiency of the drug, but of the method and low order of dosage employed.

A recent review by Seed and Jaffé (1953) has pointed out that an attempt should be made to assess dosage levels on clinical grounds, and this group has decided to proceed on such an investigation with all future patients. At the same time it is thought that some cognizance must be taken of the uptake and retention of a tracer dose of $I^{131}$

by the thyroid gland. A new dosage plan is at the moment in operation in an attempt to control hyperthyroidism with one or two therapy doses of $I^{131}$ in a total period of three to four months, but at the same time to avoid as far as possible even transitory myxœdema. This method takes into consideration the following factors: (i) Degree of toxicity in a very broad sense, as by and large this is a comparative state varying with time, a particular patient and a clinician's impressions. (ii) Uptake rate of a tracer dose of $I^{131}$ in the thyroid. (iii) Size of the gland without any further attempt to assess its actual volume accurately because of the known pitfalls and the unlikely advantages of an accurate assessment being of real advantage from patient to patient. (iv) Type of thyroid enlargement—diffuse or nodular. When it is necessary to treat the latter type, it is expected that a larger dosage is likely to be necessary than with the diffuse type, other factors being equal. (v) Correlation of levels of PBI and $PBI^{131}$ with dosage.

It is thought that, as has already been mentioned, "degree of toxicity" is only a comparative term and subject to individual interpretation, but may furnish a crude clinical subdivision by which to gauge dosage. The paradox of a patient in a severely toxic state possibly having a thyroid gland which, because of its intense hyperplasia, is more radio-sensitive than that of a patient in a less toxic state, has been noticed with patients treated with external radiotherapy and needs to be borne in mind with radio-iodine therapy.

A tentative scale of dosage offered is that seven millicuries of $I^{131}$ should be the average dose, but that: (*a*) ±1·0 millicurie be added or subtracted for a large or small gland respectively (in the case of a very large gland two millicuries are added to the "average"); (*b*) ±1·0 millicurie be added or subtracted for a mild or severe degree of toxicity respectively; (*c*) ±1·0 millicurie be added or subtracted respectively for a low uptake of a tracer dose on the one hand and a high uptake on the other. Hence, the dosage range is four to 11 millicuries.

When the problem of dosage of $I^{131}$ is on a firmer basis, this drug should offer a convenient, safe and effective means for treating thyrotoxicosis in selected cases with little or no inconvenience to the patient. The incidence of late sequelæ and late recurrences, if they are to take place, cannot as yet be estimated.

### Reports of Cases.

The following are brief summaries of the subjects treated with $I^{131}$ for hyperthyroidism. Whenever the dose in millicuries is also quoted in e.r, this is the dose in e.r calculated for the particular gland in a particular patient from the administered dose (Clarke, 1951). Details are set out in Table II.

CASE 9.—A female patient, aged thirty-eight years, presented with thyrotoxicosis, progressive exophthalmos, cardiac failure and auricular fibrillation. A small diffuse thyroid enlargement was present. A dose of 5000 e.r was planned, but only 2·1 millicuries were available (3900 e.r). There was improvement, but not complete control. After three months a dose of 3·2 millicuries of $I^{131}$ (5000 e.r) was given, and the patient's condition was non-toxic three months after this dose. It became mildly toxic again eight months later. A further therapy dose of 2·35 millicuries (6000 e.r) was given, and her condition was non-toxic when she was last examined four months after this dose.

CASE 11.—A female patient, aged thirty-three years, presented with a very large diffuse goitre and primary thyrotoxicosis. Treatment with thiourylene drugs was considered ill-advised because of the likelihood of further increase in the size of the gland. The patient did not desire surgical treatment. Her condition was moderately toxic. A therapy dose of 5·38 millicuries of $I^{131}$ was given, with marked improvement thereafter. However, eight months later her condition was considered to be still very mildly toxic, and a further therapy dose of 6·0 millicuries of $I^{131}$ was given four months ago. She is now mildly myxœdematous.

CASE 12.—A female patient, aged fifty-two years, presented with a large nodular goitre, severe thyrotoxicosis, auricular fibrillation and exophthalmic ophthalmoplegia. Surgical treatment was intended, but thiouracil and iodine medication failed to produce a safe remission. A therapy dose of 4·0 millicuries was given with improvement, but not complete control. After two months the dose of 4·0 millicuries of $I^{131}$ was repeated. In the subsequent two months there was remarkable improvement, and the gland was reduced to at least half its original size. Her physician chose to revert to the thiouracil medication.

CASE 16.—A female patient, aged sixty-three years, presented as a "thyrocardiac" with a retrosternal goitre. No goitre was present in the neck, although tracer studies suggested that the retrosternal thyroid was not the site of the hyperfunction. A therapy dose of 2·6 millicuries (estimated as 6000 e.r) of $I^{131}$ was given. The patient was euthyroid two months later. However, three months after the dose her condition was considered again slightly toxic and a further dose of 2·5 millicuries was given five months ago, and when she was last examined the patient's condition was non-toxic.

CASE 20.—A female patient, aged sixty-three years, had a subtotal thyroidectomy in 1941 for a nodular toxic goitre. In late 1950 she presented with a large recurrent goitre, essential hypertension and thyrotoxicosis. A single dose of 3·0 millicuries (6000 e.r) of $I^{131}$ controlled her condition during the ensuing two years. She now has congestive failure due to ischæmic heart disease, but there is no evidence of thyrotoxicosis.

CASE 21.—A female patient, aged fifty-one years, underwent a subtotal thyroidectomy in 1935 for thyrotoxicosis. Toxicity recurred in 1939 and she was treated medically until 1950, but her condition was not fully controlled. A single dose of 1·7 millicuries (5000 e.r) was given, with complete control for the next eighteen months.

CASE 25.—A female patient, aged thirty years, developed thyrotoxicosis with auricular fibrillation, congestive cardiac failure and exophthalmos. She had had a preexisting goitre for ten years. Preparation for surgical treatment was undertaken with methyl thiouracil and iodine. In June, 1952, she suddenly developed acute mania. An empirical therapy dose of 3·0 millicuries was given, no tracer test being possible. She improved rapidly and became quite sane, but her condition was still slightly toxic three months later. A dose of 4·7 millicuries of $I^{131}$ (6000 e.r) was given. There was continued improvement during the next six months, but very mild toxicity persisted. A third dose of 4·0 millicuries

TABLE III

*Malignant Disease of the Thyroid.*

| Case Number. | Histological Diagnosis. | Treatment of Primary Growth. | Number of Doses of $I^{131}$. | Total Dose. | Result. |
|---|---|---|---|---|---|
| M5 | Adenocarcinoma. | Already surgically removed. | 5 | 90 millicuries in 7 months. | No improvement; treatment discontinued; patient still alive. |
| M7 | Adenocarcinoma. | Already surgically removed. | 6 | 104 millicuries in 12 months. | Improved, but died from paraplegic complication. |
| M8 | Papillary adenocarcinoma. | Removed surgically and ablated with $I^{131}$. | 4 | 150 millicuries in 4 months. | No improvement; treatment discontinued; patient still alive. |
| M9 | Adenocarcinoma. | Treated by surgery and X-ray therapy. | 5 | 125 millicuries in 4 months. | ? Thyroid crisis from $I^{131}$; died without improvement. |
| M10 | Adenocarcinoma. | Surgical removal. | 8 | — | Improved; still under treatment. |

of $I^{131}$ was given in April, 1953. At the present time her condition is non-toxic.

CASE 28.—A female patient, aged forty-six years, presented with primary thyrotoxicosis of moderate severity and a small goitre. She was given an empirical dose of 5·0 millicuries. Her physician chose $I^{131}$ as the treatment of choice. There was no sign of thyrotoxicosis eighteen months later.

CASE 44.—A female patient, aged seventy years, presented with hypertension, auricular fibrillation, congestive cardiac failure and a small goitre. She had not responded to routine cardiac therapy and was diagnosed as having thyrocardiac disease. A therapy dose of 1·0 millicurie (11,000 e.r) was given, and her condition remained non-toxic until she died nine months later from other causes.

CASE 52.—A female patient, aged sixty-three years, presented with severe thyrotoxicosis, auricular fibrillation, congestive cardiac failure and exophthalmos. A dose of 7·0 millicuries of $I^{131}$ (6000 e.r) was given. Improvement was noted after one month and continued for the next four months, but there was slight residual toxicity. A further dose of 9·2 millicuries of $I^{131}$ (6000 e.r) was given at this stage. Still there was not complete control, and three months later an empirical dose of 7·0 millicuries was given.[1]

This case illustrates the difficulties of adequate estimation of dosage.

CASE 56.—A female patient, aged fifty-one years, presented with a history of a moderate enlargement of the thyroid since adolescence, with some recent increase in size in the last twelve months. She had noticed loss of weight, nervousness and sweating. Her condition was clinically considered to be moderately toxic, and the results of tracer studies with $I^{131}$ and PBI analysis agreed. An empirical dose of 6·0 millicuries was given. After three months her clinical condition was non-toxic, and further tracer studies and PBI estimations showed normal thyroid function. When she was last examined six months after the therapy dose, her condition was still non-toxic.

CASE 57.—A female patient, aged thirty-five years, was suffering from primary thyrotoxicosis and had been treated with thiouracil for nine months until she developed myxœdema. After cessation of medication for two months her condition was again toxic, and she refused further medication with thiouracil. She was given an empirical dose of 6·0 millicuries and became euthyroid.

CASE 58.—A male patient, aged fifty-two years, had severe thyrotoxicosis with a very large goitre and rapidly progressive exophthalmos. He was treated medically for eighteen months, but did not improve. The progressive nature of his exophthalmos suggested that surgical treatment might be ill advised. A dose of 6·0 millicuries of $I^{131}$ (6000 e.r) was given. His condition was still toxic one month later, so it was decided to repeat a dose of 6·0 millicuries immediately. During the next two years his condition has remained non-toxic. His goitre and exophthalmos have subsided, and he is perfectly well and engaged in heavy manual work. Adjuvant treatment included deep X-ray therapy to the pituitary fossa (a tumour dose of 3000r in one month). However, the time intervals indicated that there was no immediate relief of the exophthalmos from the X-ray therapy.

CASE 60.—A female patient, aged forty-seven years, had a recurrence of thyrotoxicosis nine years after subtotal thyroidectomy. She had thyrocardiac signs and symptoms and exophthalmos. Treatment with thiouracil did not control her condition. She was given an empirical dose of 5·0 millicuries of $I^{131}$, and when last examined six months after this dose her condition was still toxic, but had improved.

CASE 62.—A female patient, aged thirty-eight years, had a subtotal thyroidectomy in 1927 for a nodular toxic goitre. In 1940 she developed a recurrent thyroid nodule and was treated with deep X-ray therapy, with improvement. In 1950 she developed further nodules in the site of the thyroid and recurrent thyrotoxicosis with severe exophthalmos. In April, 1952, she was given 2·0 millicuries of $I^{131}$ (5000 e.r). Three months later her condition was improved but still toxic, and she was given 2·3 millicuries of $I^{131}$. This treatment was repeated five months later, when 5·0 millicuries (6000 e.r) were given. Further improvement, but not complete control of toxicity, was achieved, and three months later a fourth dose of 3·0 millicuries of $I^{131}$ was given empirically. It is as yet too soon after this dose to assess its effect.

This patient is obviously under-dosed.

CASE 63.—A female patient, aged forty-two years, presented with a goitre of five months' duration, causing thyrotoxicosis and very severe exophthalmos and ophthalmoplegia. A therapy dose of 6·0 millicuries of $I^{131}$ was given in July, 1950, and X-ray therapy to the pituitary (a tumour dose of 3000r in four weeks) in August, 1950. There was improvement during the next three months, and six months after therapy her condition was non-toxic, although some residual exophthalmos remained. Signs of toxicity were again present nine months after the dose of $I^{131}$. A further dose of 4·8 millicuries of $I^{131}$ was given. A non-toxic state persisted for a further nine months, when her exophthalmos again became alarming and a further therapy dose of 6·0 millicuries of $I^{131}$ was given. In the past eighteen months her condition has remained non-toxic. Deep X-ray therapy was given to posterior orbital tissues, but a moderate degree of exophthalmos remains.

CASE 67.—A female patient, aged fifty-seven years, presented with a six months' history of pyrexia of unknown origin, periorbital œdema, lassitude, tiredness and falling out of temporal hair. Treatment had been instituted with thyroid medication by her own doctor on the clinical assumption that she had hypothyroidism. Tracer studies with $I^{131}$, after thyroid medication had ceased for one month, suggested thyrotoxicosis. This became clinically evident one month later, when exophthalmos developed. A therapy dose of 2·0 millicuries of $I^{131}$ was given. Her condition was non-toxic four months later. Soon after this it again became toxic, and a further therapy dose of 1·78 millicuries was given. Her condition has remained non-toxic for the past eighteen months.

CASE 75.—A female patient, aged twenty-two years, presented with a large goitre and severe thyrotoxicosis. Her physician wished her to be treated with $I^{131}$. The first dose available was 6·2 millicuries (3400 e.r). Because of her degree of toxicity she had adjuvant treatment with methyl thiouracil for the next two months. Three months after the therapy dose and one month after cessation of thiouracil treatment her condition was non-toxic.

This was one of the first cases in which the degree of toxicity was such that it was considered unwise to wait until the effects of the $I^{131}$ were apparent. In addition, when the patient was first examined the size of the gland was such that surgical treatment was discussed. However, three months later the gland was no longer palpable and toxicity was minimal.

CASE 80.—A female patient, aged twenty-eight years, had a subtotal thyroidectomy in 1944 for primary Graves's disease. Further operation was necessary in 1949 for recurrence of toxicity. In 1950 hyperthyroidism was again evident, and treatment began with methyl thiouracil, but had to be discontinued when she developed hypothyroidism eight months later. Within three months her condition was again toxic, but she developed nausea, vomiting and leucopenia with methyl and propyl thiouracil. Her condition was severely toxic by March, 1951, and she was given 3·5 millicuries (5000 e.r) of $I^{131}$. Because of the degree of toxicity it was necessary to give her thiouracil one week after the radio-active iodine. Improvement was rapid, so that thiouracil therapy was discontinued two months later. There was residual toxicity four months after the first dose of $I^{131}$. A second therapy dose of $I^{131}$ was given. Toxicity was controlled for the next nine months, when symptoms again recurred. A third dose of 1·0 millicurie (11,000 e.r) was given and seven months later repeated. Her condition was non-toxic until she became pregnant five months later; 2·0 millicuries were given at the eighth week of pregnancy.

CASE 87.—A female patient, aged sixty-one years, underwent subtotal thyroidectomy for thyrotoxicosis in 1949. One year later the patient developed pre-tibial myxœdema and was treated with thyroid tablets. When examined in January, 1952, she had a history of recurrent thyrotoxicosis with exophthalmos of six months' duration. No thyroid tissue was palpable. A dose of 1·0 millicurie of $I^{131}$ was given, with some improvement. Deep X-ray therapy (a tumour dose of 3000r in one month) was given to the pituitary. Her condition was still mildly toxic six months later, and a further dose of 4·0 millicuries of $I^{131}$ was given. Her condition was still considered toxic three months later, and 3·0 millicuries of $I^{131}$ were given. For the past eight months her condition has remained non-toxic, although her exophthalmos and pretibial myxœdema persist.

CASE 100.—A male patient, aged forty-seven years, presented with hypertension, auricular fibrillation and congestive cardiac failure not responding to routine cardiac therapy. A visiting cardiologist of international fame, after examining the patient, suggested that there might be a masked thyrotoxicosis. Tracer studies with $I^{131}$ confirmed this. A therapy dose of 2·1 millicuries of $I^{131}$ (5000 e.r) was given, and the cardiac failure was responsive to routine therapy for the

[1] Four months prior to the writing of this paper.

next eight months, when the patient died as a direct result of his hypertension.

CASE 116.—A female patient, aged fifty-one years, had had treatment for thyrotoxicosis with deep X-ray therapy twenty-three years previously, and was referred for $I^{131}$ therapy. Subsequently she developed severe radio-dermatitis of the overlying skin. In 1946 she developed recurrent thyrotoxicosis and was treated with thiouracil. This drug had to be stopped because of drug toxicity. Surgical treatment was not advisable because of the tissue damage from prior irradiation. A therapy dose of 3·2 millicuries of $I^{131}$ was given, with improvement, but not complete control. After six months a second dose of 4·0 millicuries of $I^{131}$ was given. Her condition has now been non-toxic for three years.

CASE 117.—A female patient, aged fifty-two years, presented with mitral stenosis and incompetence, gross cardiac failure and auricular fibrillation, rheumatic in origin. In addition a thyrotoxic element was considered to be present. An empirical dose of 3·76 millicuries of $I^{131}$ was given, but after this she showed no improvement, and died from cardiac failure two months after the therapy dose was given.

### INVESTIGATION OF MEDIASTINAL MASSES WITH $I^{131}$.

The possibility that a superior mediastinal tumour may be a retrosternal thyroid mass is always uppermost in the mind of a clinician. With $I^{131}$ tracer tests available a new method became practicable for investigation of such tumours.

TABLE IV.
*Tracer Doses of $I^{131}$.*

| Case Number. | Result of Histological Examination. | Primary Tumour. | Metastases. | Result Tracer. |
|---|---|---|---|---|
| M1 | Adeno-carcinoma. | Removed surgically. | Cervical nodes. | No significant uptake. |
| M2 | Indefinite type. | Present. | Lungs and bones. | No significant uptake. |
| M3 | Papillary adeno-carcinoma. | Present. | ? Glands and bones. | No significant uptake. |
| M4 | Adeno-carcinoma. | Removed surgically. | Cervical nodes. | No uptake. |
| M6 | Papillary adeno-carcinoma. | Present. | Cervical nodes. | No significant uptake; operation undertaken. |
| M11 | Indefinite (anaplastic). | Present. | Cervical nodes and lungs. | No significant uptake. |
| M12 | Not made. | Probably from breast. | Bones, probably metastatic from carcinoma of breast. | No uptake. |
| M13 | Anaplastic. | Removed surgically. | Cervical nodes; bilateral pulmonary metastases. | No uptake. |

A total of ten cases of mediastinal masses was investigated, to determine whether there was any evidence of functioning thyroid tissue. One of the difficulties with tracer doses of $I^{131}$ is the close proximity of the superior mediastinum to the thyroid normally situated in the neck. Physical measurements are likely to be influenced by stray radiation from this site. Moreover, early surveys may indicate significant uptake of $I^{131}$ in the region of a very vascular mediastinal mass because of intravascular circulating $I^{131}$. This difficulty can be overcome by making surveys at longer intervals, provided a sufficient tracer dose of $I^{131}$ is given.

Notwithstanding these difficulties, in six of the ten patients tested there was sufficient discrete uptake in the mediastinal mass to indicate the thyroid tissue content. This conclusion was later verified at operation on each of these six patients. In the remaining four patients there was no evidence of uptake of tracer doses of $I^{131}$. One patient was considered to have a retrosternal goitre with hyperthyroidism, but the mediastinal mass did not appear to concentrate $I^{131}$, so that the hyperthyroidism was considered to arise from thyroid tissue in the neck.

A further patient in whom $I^{131}$ failed to be taken up was proved at operation to have a neurofibroma. Another proved to have a teratoma.

A final diagnosis was not established in the remaining case, but the later development of carcinoma of the larynx suggested this mass was due to metastases. It is considered that the simple procedure of investigating such mediastinal masses with tracer doses of $I^{131}$ when the diagnosis is in doubt is a worthwhile measure. Lack of uptake does not necessarily exclude the presence of a thyroid mass, but when significant discrete uptake is detected in the mass it is presumptive evidence that it contains thyroid tissue.

### MALIGNANT THYROID DISEASE AND $I^{131}$.

External X-ray therapy is an established method of palliative treatment for carcinoma of the thyroid. When $I^{131}$ began to be used clinically, it was hoped that it might prove a useful weapon with which to treat metastatic malignant disease of the thyroid. Frantz *et alii* (1944) first reported on the uptake of $I^{131}$ by a metastatic deposit from carcinoma of the thyroid. It soon became apparent that the histological type of the tumour and the presence or absence of the thyroid gland were important factors in deciding on the use of $I^{131}$ for malignant disease.

Fitzgerald, Foote and Hill (1950) took radioautographs in 100 cases of carcinoma of the thyroid, and showed that therapy with $I^{131}$ could not offer much benefit except with a well-differentiated tumour. Thereafter biopsy of the primary growth or its metastases, autoradiography and tracer tests with $I^{131}$ became important investigations of patients with carcinoma of the thyroid for whom therapy with $I^{131}$ was considered. It is now established that whenever possible total thyroidectomy or ablation of thyroid with large doses of $I^{131}$ is necessary before significant uptake of $I^{131}$ in distant metastases can be expected. Even then, unless the metastases are well differentiated and functionally active, such therapy is generally expensive and futile.

Some clinics are investigating the possibility of influencing differentiation of malignant metastases of the thyroid with thiouracil derivatives and thyrotrophic hormone after total thyroidectomy has been performed (Marinelli *et alii*, 1951). No such opportunity has been given to this group. Experience with $I^{131}$ as a therapeutic agent in this series is very limited. In all, 17 patients with known or suspected carcinoma of the thyroid were examined. These were eventually dealt with as follows: (i) Four patients had $I^{131}$ for autoradiography only and were not accepted for $I^{131}$ therapy (Cases 14, 15, 16, 17). (ii) Eight patients had tracer studies with $I^{131}$ and were considered not suitable for $I^{131}$ therapy (Cases 1, 2, 3, 4, 6, 11, 12, 13). (iii) Five patients had therapy doses of $I^{131}$ (Cases 5, 7, 8, 9, 10).

In each case investigated by autoradiography, histological examination of the tumour revealed anaplastic or papillary carcinoma, and the uptake of $I^{131}$ was seen to be minimal and "spotty". It was considered that therapy doses of $I^{131}$ could not be expected to offer much benefit. Each of the eight patients who had tracer surveys with $I^{131}$ is reported below. Adenocarcinoma, poorly differentiated or papillary in type, was the tumour type in four cases (Cases 1, 3, 4, 6). One patient after further investigation was considered to have metastatic carcinoma of the breast rather than carcinoma of the thyroid (Case 12). In the remaining three cases the pathological condition was indeterminate. It will be seen from reading the brief summaries that in each of the cases in which tracer tests with $I^{131}$ were performed, the degree of uptake in primary tumour or secondary deposits, even after surgical removal of the primary had been carried out in some cases, was insufficient to allow any therapeutic effect from $I^{131}$ to be expected.

General conclusions of overseas clinics regarding radioactive iodine therapy for carcinoma of the thyroid (Seidlin

*et alii*, 1948; Warrington, 1950; Beierwaltes, 1952; Egmark *et alii*, 1953) suggest the following:

1. Significant uptake of $I^{131}$ sufficient to offer therapeutic benefit is to be expected usually only with well-differentiated adenocarcinoma of the thyroid showing follicle formation. A small biopsy specimen may give an erroneous impression of the major histological features of the tumour or its metastases.

2. Even when the primary growth is very well differentiated, it does not follow that the metastases will show the same degree of differentiation.

3. There may be uptake of $I^{131}$ to a degree in some cases of papillary adenocarcinoma.

4. Uptake of $I^{131}$ in anaplastic and so-called "hurtle cell" growths is minimal or absent.

5. Occasionally total thyroidectomy by surgery or ablation with large doses of $I^{131}$ followed by administration of thiouracil and thyrotrophic hormone may aid in differentiation of metastases.

6. The Standing Committee on Radio-isotopes of the National Research and National Health Council have laid down the policy that for the time being $I^{131}$ should be made available only for treating selected patients with well-differentiated carcinoma of the thyroid.

The clinical histories of patients with carcinoma of the thyroid treated with radio-active iodine are briefly discussed below. The unusual sequel of a thyroid crisis arising in a patient with metastatic malignant thyroid disease is therein reported.

### Records of Patients Treated with $I^{131}$.

CASE M5.—A female patient, aged seventy-two years, developed recurrent adenocarcinoma of the thyroid in supraclavicular glands nine years after a subtotal thyroidectomy. When she was examined she had pulmonary and skeletal metastases. Tracer studies showed that there was still significant uptake in residual thyroid tissue in the neck. There was no uptake in the metastases. The treatment policy was to ablate residual normal thyroid tissue with therapy doses of $I^{131}$, in the hope that metastases might then show differentiation. During the next seven months a total of 90 millicuries of $I^{131}$ was administered. There was progressive decrease in the uptake of $I^{131}$ in the neck and increase in uptake in the metastases. Limited supplies of $I^{131}$ prevented further dosage. There was no clinical or radiographic evidence of improvement up to the time of cessation of $I^{131}$ therapy.

CASE M7.—A female patient, aged sixty-two years, had a subtotal thyroidectomy for an "adenoma" of the thyroid. After an interval of ten years she presented with "fairly well differentiated adenocarcinoma of the thyreoid", metastatic in cervical glands and bones. Collapse of the seventh dorsal vertebra from malignant infiltration had caused paraplegia. Tracer studies with $I^{131}$ suggested that at least 50% of the dose was trapped by metastases. During the next twelve months a total dose of 104 millicuries of $I^{131}$ was given in fractions varying from 10 to 40 millicuries. There was progressive reduction in size of the malignant metastatic cervical nodes and also in a subcutaneous area of malignant infiltration overlying the involved dorsal vertebræ. The patient died from renal complications associated with paraplegia.

CASE M8.—A female patient, aged thirty-seven years, presented with a proven papillary adenocarcinoma showing some well-differentiated vesicles. Massive malignant infiltration of the lungs was present on radiographic examination. The treatment policy decided on was to perform total thyroidectomy and endeavour to treat the metastases with $I^{131}$ if favourable uptake was noted. A tracer dose of $I^{131}$ two weeks after operation indicated that there was still significant uptake in the thyroid area. It was, therefore, necessary to use $I^{131}$ to ablate residual thyroid gland. In the next four months a total dose of 150 millicuries of $I^{131}$ was administered. There was progressive reduction in the uptake of iodine in the neck and increase in the uptake in the lung metastases. There was no evidence of radiographic change in the lungs. Supplies of iodine being limited, no further $I^{131}$ was given. The patient is *in statu quo* twelve months later. Radiographs failed to reveal any reduction in the size or number of the metastatic deposits in the lungs.

CASE M9.—A female patient, aged thirty-five years, underwent subtotal thyroidectomy for thyrotoxicosis in 1947. Histological examination of the specimen failed to reveal evidence of malignant change. A thickening in the operation scar was noted six months later and was considered to be a keloid. Because of some increase in size, a biopsy was taken from it twelve months after operation. The report on the specimen was as follows: "Infiltrating carcinoma of the thyreoid with much adenomatus hyperplasia and some sheets of undifferentiated cells." Regional X-ray therapy was given to this area of local recurrence. Metastatic malignant deposits were noted in skeleton and lungs after a further interval of six months. Tracer studies with $I^{131}$ in September, 1949, showed considerable uptake in the recurrent mass in the neck and in metastases. Therapy doses were given as follows: (i) 60 millicuries of $I^{131}$ intravenously in November, 1949; (ii) 41 millicuries of $I^{131}$ intravenously in January, 1950; (iii) 4·6 millicuries salvaged from the urine in February, 1950.

The patient returned to another State and was not examined again for three months. Metastatic deposits had increased in size at this period. A further dose of 10·0 millicuries of $I^{131}$ was available and given intravenously. Within thirty-six hours the patient developed a high fever, profuse sweating, dehydration, emotional disturbance, tachycardia, palpitations and vomiting. The sleeping pulse rate was 96 per minute. The basal metabolic rate was +34%. She was considered to have developed a thyrotoxic crisis of moderate degree from sudden liberation of excess thyroxine precipitated by the action of $I^{131}$ on functioning metastases. Symptoms were controlled by the general medical management of a thyroid crisis. A further dose of 10 millicuries of $I^{131}$ was given one month later without untoward effect. No significant relief of the metastases was noted, and the patient continued treatment with external irradiation in Adelaide until she died.

CASE M10.—A male patient, aged thirty-four years, developed weakness in the legs and backache eight months prior to being examined. Pain in the right shoulder developed one month later. Radiographs showed osteolytic metastatic deposits in the upper part of the right humerus, the sacral promontory and the ilium. A hard, irregular enlargement of the left lobe of the thyroid was noted. The report on a biopsy was as follows: "A well-differentiated carcinoma of the thyreoid with many colloid-filled vesicles." Tracer studies with $I^{131}$ showed some uptake in the metastases in bone. Surgical total thyroidectomy was performed. One month after operation tracer studies showed no uptake of $I^{131}$ in the neck, but an increased uptake in the secondary deposits in bone. Therapy doses of $I^{131}$ were given. A total dose of 538 millicuries of $I^{131}$ has been given up to date over a total period of six months, at four-weekly intervals. Amounts of up to 20 millicuries of $I^{131}$ were salvaged from the urine and retaken by the patient. After three months the patient had great relief of pain in the metastatic bone deposits, and tracer tests showed increased uptake in the metastases. Radiographs showed slight reduction in the size of metastatic deposits in the humerus and sacrum. Treatment is proceeding.

This case will be reported in full at a later date.

### Patients Not Accepted for $I^{131}$ Therapy.

Radioautographs were performed on four patients. In all cases it was considered that there was insufficient uptake of $I^{131}$ to warrant therapy with this drug. One specimen showed papillary adenocarcinoma, another was very anaplastic, and in the other two cases the tumour histologically was mainly undifferentiated.

The following are brief reports of eight patients on whom tracer tests were performed with $I^{131}$:

CASE M1.—A female patient, aged twelve years, had adenocarcinoma of the thyroid and secondary deposits in cervical nodes. Tracer tests both before and after thyroidectomy showed no significant uptake in metastases; treatment with $I^{131}$ was considered contraindicated.

CASE M2.—A male patient, aged fifty-seven years, had carcinoma of the thyroid with indeterminate histological features. Metastases were present in the lungs and skeleton. Tracer doses of $I^{131}$ showed no significant uptake in either primary growth or secondary deposits.

CASE M3.—A female patient, aged twenty-seven years, had papillary adenocarcinoma of the thyroid gland and metastases. Tracer doses of $I^{131}$ indicated insufficient uptake to warrant therapy.

CASE M4.—A male patient, aged thirty-eight years, had surgical removal of an adenocarcinoma of the thyroid and post-operative deep X-ray therapy. Recurrence developed in cervical nodes. Tracer studies showed no uptake in these nodes.

CASE M6.—A female patient, aged sixty-nine years, had papillary adenocarcinoma of the thyroid gland and cervical nodes. Tracer studies with $I^{131}$ showed little or no uptake. Surgical treatment was advised. The patient remains free of recurrent or residual neoplasm fifteen months after operation.

CASE M11.—A male patient, aged seventy-three years, had carcinoma of the thyroid with metastases in cervical nodes and lungs. Tracer studies showed no significant uptake of $I^{131}$. Palliative X-ray therapy was arranged.

CASE M12.—A female patient, aged fifty-five years, developed a large solitary osteolytic metastasis in the left ilium two years after a radical mastectomy for carcinoma of the breast. The site of operation was clear and all other drainage areas were clear. The solitary metastasis was pulsatile. A small, firm nodule was palpable in the isthmus of the thyroid gland. A tracer dose of $I^{131}$ showed no uptake in the metastasis. Further observation of the thyroid nodule for a period of several months suggested that it was benign. All general investigations failed to reveal any other primary growth. It is assumed that the metastasis probably arose from the original breast carcinoma.

CASE M13.—A female patient, aged fifty-two years, had a goitre present since adolescence. In 1947 she had a total thyroidectomy for a proved anaplastic carcinoma of the thyroid. A recurrence appeared in cervical lymph nodes three years later. A tracer dose of $I^{131}$ showed no uptake in the recurrent mass or in pulmonary metastases. She was treated with deep X-ray therapy, but died six months later.

## SUMMARY.

1. A report is given of experience with $I^{131}$ tracer studies in thyroid disease, estimation of PBI and therapy with $I^{131}$ carried out as a joint project in Melbourne.

2. The physical indices $k_1$ and U25-U15 are considered to be valuable in aiding diagnoses of hyperthyroidism.

3. PBI estimation is shown to give an accurate assessment of thyroid function.

4. Results of treating 23 patients with hyperthyroidism by $I^{131}$ are reported.

5. The investigation of six patients with mediastinal tumours is recorded.

6. Consideration of $I^{131}$ therapy for malignant disease of the thyroid is discussed. The records of five patients treated with $I^{131}$ are given.

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## THE REASON FOR CORONARY ATHEROMA[1] AND OCCLUSION.

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THIS paper is an attempt, however meagre, to present the prevailing and conflicting viewpoints of atherogenesis, in the hope, if not the expectancy, of arriving at a working concept for the basis of coronary atheroma, its detection, its prevention and, if already established, its control.

Mortality statistics, at least in the western world, suggest that coronary artery disease is increasing. However, this assumption is subject to certain critical analysis. There is, for example, the changing fashion of stating the disease entity on the death certificate form; heart failure and myocardial degeneration in many instances are now relegated to the effect and not the cause as in the case of coronary atheroma. Further, since the conquest of infectious disease with antibiotics and chemotherapy, advances in hygiene and public health, pre-natal, post-natal and maternal care, anæsthesia and surgical technique *et cetera*, there has been a steady trend towards increase of life expectancy. The natural result is an added number of middle-aged people, in whom the incidence of coronary disease would be increased.

There is now a considerable awareness in the public mind of the coronary occlusive death. In some exclusive circle one learns of a "coronary club", which has its self-appointed president, and where an air of raillery is tempered with a varying degree of philosophical resignation to the inevitable, fostered no doubt by a sense of medical ineptitude; a complacency heightened by each "successful" candidate for membership and ruffled in turn by the final exitus of a colleague with a further coronary episode.

In a less privileged group there is the wage earner in a heavy industry who is suddenly stricken in his working time, perhaps over his morning tea or a mug of beer. After a stormy recovery he finds moral comfort in the thought —which gains impetus through union and legal connivance —that he is the victim of circumstances arising out of his work (rather than, as is usually the fact, preexisting disease). His rights to compensation are enhanced by a medical opinion, and to his physical incapacity is added a cardiac neurosis. Though he may survive for years, he is denied the dignity of some employment, and thus the community pays for added social and insurance service.

In the life assurance field there is the unpredictable coronary death. The medical officer may have the required clinical and electrocardiographic wisdom and may be aware that a certain accorded "first-class risk" could be dead of a coronary occlusion before the second premium is due. He may be aware of modern aids for assessment, such as the particular somatotype, a fat tolerance test, a coronary atherogenic index *et cetera*. Current research suggests that recourse to these procedures may be helpful in anticipating the subject prone to coronary occlusion.

In the light of the foregoing reflections the idea has evolved to sort out and, where possible, integrate experimental data from authoritative sources. The connotation "coronary" has been used in the title because of its wider professional and public interest and from choice of the most convenient reference for the suggested mechanisms of thrombogenic atheroma.

### HISTORICAL SUMMARY.

The term "arteriosclerosis" was coined originally by Lobstein of Strasburg in 1833 to denote hardening and thickening of the arteries. Though Mönckeberg's medial circular sclerosis with calcification would come under this definition, atherosclerosis—the word coined by Marchand in 1904—is an entirely different disease. There is proof of its existence as the result of studies of mummies thirty-five centuries ago, so that any hypothesis as to the ætiology of atherosclerosis would require to have been valid over all that time. Rokitansky in 1852 put forward the encrustation hypothesis—namely, that atheroma resulted from fibrin deposited on the inner lining of blood vessels. This theory was upset a little later by Virchow, who taught that the fatty substances found in the intima were due to degeneration resulting from patches of hyperplasia. It was only in the second decade of this century that coronary pain was associated with the disease through the pioneer work of Herrick.

### DEFINITION OF ATHEROMA.

The lesion or plaque is focal and confined to the intima, and consists of a patchy and irregular fibrohyaline thickening, splitting of the elastic layer, and deposition of lipids, both intracellular and extracellular. The lipid accumulations comprise mainly cholesterol and cholesterol esters. The plaques are yellow in colour and may bulge into the lumen; they may undergo necrosis, with or without hæmorrhage, and ultimate calcification. The lesions may vary in respect to three components—total lipid content (atheroma), the minerals calcium and phosphorus (calcification), and the total protein content (sclerosis). This method of assessment of the degree of coronary atherosclerosis has been attempted in place of the morphological method.

### THEORIES TO ACCOUNT FOR ATHEROSCLEROSIS.

There are two main theories to explain atherosclerosis: (*a*) the disturbed lipid-cholesterol hypothesis; (*b*) the thrombogenic theory.

#### The Lipid-Cholesterol Hypothesis.

The lipid-cholesterol hypothesis of the cause of atherosclerosis revolves mainly around (i) a state of hypercholesterolæmia or hyperlipæmia due to disturbed metabolism, (ii) local factors influencing the deposition of cholesterol or lipid in the intima.

#### *Hypercholesterolæmia.*

The influence of dietary cholesterol in inducing hypercholesterolæmia is now a less vexed question. When atherosclerosis was experimentaly produced by feeding cholesterol to the rabbit it was thought that this state of hypercholesterolæmia accounted for atherosclerosis in the human being. Experimental atherosclerosis, started simultaneously by Anitschkow, and by Walker and Hueck in 1913, merely served to show that the herbivorous animal cannot metabolize cholesterol—it can absorb but not excrete it. The chick was chosen for similar experiments because it is an omnivorous creature. An objection to the validity of these findings was one to the effect that the amount of cholesterol fed to the rabbit and chick was abnormally, even fantastically, high compared with the amount of cholesterol in the

[1] "Atheroma" and "atherosclerosis" will be used interchangeably throughout.

average human diet. For example, in man the serum cholesterol level is little affected over a range of cholesterol intake from 0 to 700 milligrammes, whereas animals are given an amount equivalent to 12,000 milligrammes in man, which suggests that cholesterol in average human diets is unimportant. This objection was met by producing atherosclerosis in the chick with minimal hypercholesterolæmia; thus Katz stated "that cholesterol is the offending agent in atherosclerosis and that without an altered lipid-cholesterol metabolism little or no atherosclerosis will occur regardless of any other alteration in the arterial wall, including senescent changes". Yet, in the same paragraph he says that he does not mean that there is no other way of producing atherosclerosis and hence, I suppose, the "little or no" above.[1]

Keys's findings and views on the subject of this paragraph are worth recording in some detail. Men were studied for four months on diets beginning and ending with 150 grammes of fat and 700 milligrammes of cholesterol. By varying the fat, such as vegetable fat, and keeping the cholesterol, such as egg yolk, anywhere between zero and 500 milligrammes, he came to the conclusion that the serum cholesterol level in adult man is independent of the cholesterol intake over the range of zero to 700 milligrammes daily, but that the fat intake is quite another matter, and appears to have great importance in perpetuating and increasing the level of serum cholesterol. He goes on to say that the inferences to be drawn from this dietary effect on atherosclerosis would be similar if the criteria were related to the percentage amounts of certain lipid fractions, such as the $S_f$10-20 macromolecules in the serum.

The same authority states that it has not been proved that human atherosclerosis results from the ingestion of cholesterol and/or fat; yet he agrees that it is probable that human atherosclerosis is caused by the ingestion of cholesterol and/or fat, and if mankind stopped eating eggs, dairy products, meats and all visible fats, he believes that atherosclerosis would become rare.

Research by Duff and McMillan went to show that hypercholesterolæmia is not the sole factor concerned in the genesis of experimental atherosclerosis. Rabbits fed cholesterol were first rendered diabetic by a diabetogenic agent, alloxan, and compared with controls similarly fed. Though the same amount of hypercholesterolæmia was produced in each case and the lipæmia was more visible in the diabetic rabbits, the extent of atherosclerosis produced in the latter was less than in the controls. It was concluded that hypercholesterolæmia and hyperlipæmia had no direct application to the atherosclerosis found in the diabetic, that there is "some unknown factor governing the process of lipid deposition in the walls of arteries".

In somewhat similar vein is the work of Blumgart, who followed up the cases in which total thyroidectomy had been performed for heart failure. Some of these patients had myxœdema with resultant hypercholesterolæmia for thirteen years, yet their coronary arteries at autopsy were not found to be abnormally atherosclerotic.

Leary, over the years, has remained a staunch protagonist of the metabolic theory of atherosclerosis, and regards crystalline ester cholesterol as an irritant like silica. His concept is based on evidence obtained after a long period of cholesterol feeding to the rabbit. He was able to demonstrate cholesterol-laden foam cells in the hepatic vein and the pulmonary capillaries, and postulated that the cholesterol after absorption was taken up by the Kupffer cells of the liver, then through the lungs to the systemic vessels. These cholesterol-laden cells, by virtue of their stickiness, cling to the endothelial surface at points where each heart beat is halted and eventually burrow under the endothelium, the sequel being fibrosis, scarring, necrosis and calcification. Gordon is in agreement with this concept, and has added certain refinements in respect to the greater incidence of atheroma in the elastic arteries and the location of the lesions. His view is that, with each pulsation, ebb and flow and eddying of the blood-stream occurs, especially where there is branching and forking of the arterial channel. The large and lighter lipophages gravitate to the outer part of the stream, are forced into the thicker intima and trapped by the elastic membrane. These conditions do not obtain in the less elastic vessels, so that the lipophages, if they do enter the inner wall, are free to pass through to the venules of the adventitia.

Duff's further views are pertinent to the last paragraph. He agrees that the amount of cholesterol found in the intima is too large to be accounted for through local breakdown of tissue, and that it must have been derived from another source and deposited there. Nevertheless, he believes that a state of hypercholesterolæmia is not necessarily responsible for the cholesterol deposit in the intima of the human except when the stability of the cholesterol in the plasma is affected in some way, as by the metabolic habitus of the subject; further, that the earliest lesions in the experimental rabbit are aggregations under the endothelium of "foam" cells filled with lipid, which is also extracellular, but there is complete absence of fibroblastic material; again, whereas the reversibility of these lesions has a resemblance to that of the fatty streaks in the early atheroma of man, in the latter the fibrous thickening occurs without a trace of lipid. Leary accounts for this on the basis of greater metabolic activity in the rabbit than in man.

Space does not permit of other than a passing review of Gofman's work. However, it should be stated that his original concept of a specific macromolecule of the serum in a coronary prospect has now been expanded to devise what is called a "coronary atherogenic index" whereby the susceptibility of an individual to coronary occlusive disease may be predicted according to the percentage amounts of certain lipo-protein molecules in his or her serum as shown through flotation with the high speed ultracentrifuge. In a series of nearly 2500 people of both sexes, this group at Berkeley, California, has worked out an average "atherogenic index" which they state is in clinical accord with normals, coronary heart subjects, diabetics and hypertensives. It might be mentioned here that Gofman does not regard these cholesterol-bearing lipo-protein molecules as having any relation to the chylomicrons of alimentary lipæmia, nor does he accept the theory, set out above and to follow, of the macrophage transport of cholesterol or lipid. Cholesterol was fed to rabbits after a radioisotope had been injected intravenously. Subsequently the rabbits were sacrificed and the radioactivity was found to be low in relation to the amount of atheroma present. India ink was used to confirm these findings.

### *Manner of Entry of Cholesterol into the Intima.*

Theory abounds in the physico-chemical concepts of cholesterol atherosclerosis. Hueper suggests that intravenous injections of macromolecular substances formed a film at the plasma and endothelial interface, producing in this way anoxia of the intima. Moreton's work continued on the lines that the physical state of the lipid molecules in the serum should be studied rather than their concentration as in the case of the $S_f$10-20 lipoproteins—that, in other words, it is the size of the lipid particles that determines their deposition in the intima. It will be suggested, or agreed perhaps, that this is another way of expressing Gofman's dictum. However, Moreton affirms that alimentary lipæmia is the crux of the situation; that the cumulative effect of many fatty meals over a lifetime, by producing transient showers of large lipid particles in the plasma, is the underlying cause of atherosclerosis. His suggestions seem attractive and to merit treatment in a little detail. His proposition is that, since oil and water do not mix, the lipids in the plasma are in molecular or colloidal complexes; cholesterol and fatty acids are carried together after absorption from the intestine, taken up by scavenger or reticulo-endothelial cells and transuded into the intima along with the nutrient plasma lymph. The finer lipid particles wander out to the lymphatics and venules of the adventitia, the larger being retained as

[1] In a recent publication Katz (Katz *et alii*, 1953) would appear to have modified his views, for he stated that "there is a wide range of values for total cholesterol, Sf12-20 concentration and cholesterol phospholipid ratios in normal subjects and those with hypertension, diabetes and coronary disease and that the significance of any value found should be interpreted cautiously".

foam cells. The fatty acid part is easily resorbed, the cholesterol, less so, remains trapped in the intima.

Further evidence for the molecular-colloidal theory has been provided by the intravenous injection of cholesterol, which explains, it is suggested, why atheroma may be extensive even with minimal hypercholesterolæmia.

Evans *et alii* brought evidence in support of this view by pulsating blood of atherosclerotic individuals against non-atherosclerotic aortic strips. Their postulate was in accord with that previously mentioned—that there is a continuous transudation of plasma through the walls of arteries, and that this is returned to the circulation by perivascular vessels and lymphatics, the lipid molecules of greater size becoming enmeshed in the intima.

### *Unusual Cholesterol Views.*

Cast in a different mould from the foregoing are the following hypotheses.

Thanhausser believes that atherosclerosis, other than the xanthomata *et cetera*, results through the fibrillary elastic tissue of the artery being broken up through wear and tear, the cholesterol and calcium being precipitated secondarily as the result of a physico-chemical reaction, and that any foam cells result from imbibition by macrophage cells of the sclerosed wall. The conclusions of Lansing *et alii* are allied to this view. They bring evidence to show that cholesterol deposition in atherosclerosis of the intima is secondary to elasto-calcinosis or aging of the medial elastic tissue, which has no relation to Mönckeberg's medial calcification. This elasto-calcinosis is impalpable and invisible and revealed only by special chemical analysis, and may reach high dimensions while the amount of cholesterol is still low.

Dock has introduced what might be called the why of the matter. His theory is that the focal lesions of atheroma, such as calcium and cholesterol, may occur as a result of local injury, hæmorrhage or necrosis; also that atheroma is found in certain sites, such as the epicardial parts of the coronary arteries, the division of the abdominal aorta *et cetera*, because of what he is tempted to view as a "churning" action of collagen fibres, which vibrate under a rise of pressure and so literally churn out the cholesterol from the interstitial fluid. It is certainly ordinary knowledge that atheroma of retinal arteries is usually associated with some degree of diastolic hypertension. The same author believes that thickness of the intima may be important, whether innate or acquired, and points to the fact that men have a thicker coronary artery intima than women, an aspect that was brought to light recently in post-mortem examinations on Korean soldiers.

### *Experimental and Clinical Atherosclerosis.*

The idea has been evolved that in cholesterol-induced atherosclerosis the reticulo-endothelial system becomes saturated with cholesterol, and that under favourable conditions, such as a damaged endothelial lining, the cholesterol seeps through along with the nutrient fluid from the plasma and is deposited in the intima. However, there is considerable weight of evidence against the identity of experimental and clinical atherosclerosis. Moon and Rinehart took for their material the coronary arteries of 250 people who had died suddenly from traumatic or natural causes without any history of preceding illness, the ages ranging from four months to ninety years. Their purpose was to determine the sequence of histological changes in the development of coronary atherosclerosis. Their findings suggested that the deposition of lipid is not the initiating factor. It was their impression that the *vasa vasorum* were more likely the source of any exogenous lipid in sclerotic plaques than transintimal inbibition of lipid from the lumen, because lipid was found at the base of the plaque and not at the endothelial border. More recently Dock and Moschowitz have pointed out that intimal hyperplasia and lipid deposition are separate pathological entities, though lipid changes may occur in preexisting fibrous plaques.

### Thrombogenic Atheroma.

The presentation of the thrombogenic hypothesis in relation to atheroma has been motivated for two main reasons. At a congress the writer attended in Chicago in 1950 on arteriosclerosis, all discussion centred around cholesterol-lipid metabolism as the main if not the only factor in atherosclerosis. Contention was rife and unwarranted assumption got short shrift, not usually because the factual was in question, but rather because of the conclusions arising therefrom. Deductions drawn from some exquisite piece of research at the experimental level would be assailed, since, as it was said, man in his metabolic habitus was not a bird, a rabbit or a dog. The points at issue were mainly how, when, whence and why the lipids found their way into the intima of arteries. Gofman was the guest speaker, and as such enjoyed relative immunity. The atmosphere, in fact all America, was agog with his hypothesis of the large cholesterol-bearing lipoprotein molecule as being the pathognomonic entity in the candidate for a coronary occlusion, and the thought occurred: what a pity the ultracentrifuge was such a costly aid for this assumption. All was cholesterol. I have a hazy recollection of somebody away from the forum mentioning a man who sponsored the idea that the atheromatous plaque arose from the endothelial surface in some way and became eventually engulfed in the intima. Viewed in retrospect, the reference was to Duguid's work, designed to show that a mural thrombus was, at least in a great percentage of cases, the starting point for the atheromatous plaque. The grounds for this mechanism were supplemented by Magarey in the case of the thickening of heart valves.

The other reason for ventilating this hypothesis centres around that of surprise and challenge, the former in that in the United States of America literature it is relatively unheard of, the latter because in the view of the writer it provides not only a plausible explanation for the histology and chemistry of atheroma, but a logical background for the clinical integration of the varied coronary pain syndromes and their management. The accompanying diagram (Figure I) is tendered to indicate the suggested mechanisms.

After the experimental phase of the study of cholesterol-induced atherosclerosis by Anitschkow came the work of Winternitz, who demonstrated the *vasa vasorum* of the intima of vessels. Though evidently he went a little far in accounting for their part in atherogenesis, the recognition of these channels provided a concept for the understanding of clinical syndromes of atheromatous lesions. The long prevailing view of atheroma as an intimal overgrowth of tissue with fatty degeneration and necrosis, cholesterol and calcium deposition, whilst histologically acceptable, has a limited application in the integration of anginal syndromes.

In 1852 Rokitansky put forward the view that atheroma resulted from "an endogenous product derived from the blood and for the most part from the fibrin of the arterial blood". The initiative has been taken by Duguid to link up this theory with Winternitz and develop it further. The idea occurred to him that the structural changes in the intima in atherosclerosis, such as fibrous overgrowth and fatty deposits, should lessen the elastic recoil of the artery, thereby weaken the wall and so result in widening rather than narrowing of the artery. His postulate is that in many instances the lesions now classed as atheroma arise from thrombi deposited on the walls of vessels. These thrombi in process of retracting become covered over though spread of the endothelial lining and incorporated in the intima as an atheromatous plaque. The ultimate fate of the plaque would depend on the size of the mural thrombus, whether it was pale or red, and on the extent to which, if at all, it became vascularized from the lumen or transmedially by capillary extension from the *vasa vasorum*. Organization of the plaque might be so complete that its origin from the original thrombus might be concealed, the end result being the lesion ordinarily found in atherosclerosis — for example, fibrous and fibrohyaline thickening, fatty and hæmorrhagic necrosis, calcium and cholesterol deposits. It is thus probable that many of the blood patches on the aorta *post mortem* would be found

to be thrombi in varying stages of organization and not merely post-mortem deposits. The tendency in the past has been to regard atherosclerosis as merely a physiological process of aging or reactionary intimal hyperplasia. The concept of thrombogenic atheroma as having relation to factors governing fibrin formation in the blood appears at first sight to be the very antithesis of traditional concepts. Later it will be suggested that this is not quite so.

### Other Research Considerations.

Inseparable from and relevant to the previous hypotheses are the following for consideration.

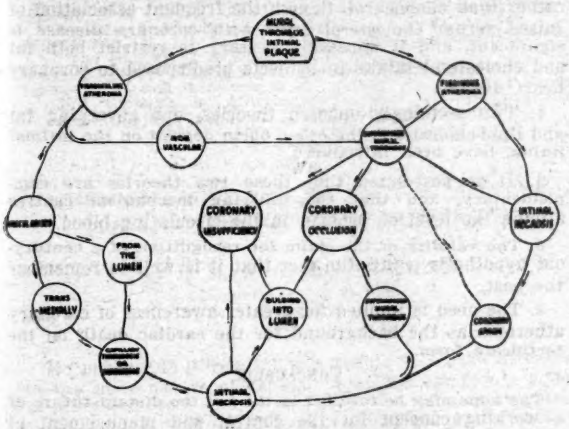


Figure I.

Thrombogenic atheroma. This diagram has been designed to embrace the encrustation theory of Rokitansky (1852), resurrected with emendations by Duguid (1946) and with the vascular physiology of the *vasa vasorum* of Winternitz (1937). Amplification would require a separate treatise. The interrupted line has been used to indicate that, whereas coronary spasm may occur from irritation of the muscle layer in intimal necrosis, it would be less likely in superimposed mural thrombus.

### Geographical Considerations.

Sweden was chosen by Henschen some eighteen years ago to explore this factor in atherosclerosis, especially as its people are a homogenous race, yet widely separated through climatic circumstances. Thus in the far north the winters are long and cold and the diet is mainly lacto-vegetarian, containing fish and relatively little fat; in the middle (Stockholm) and the south the climate is equable and the diet is varied and liberal. Autopsies were performed with due regard to number and accuracy, and it was found that in the north there was little atheroma compared to the south. Further to this is the fact that during the nutritional restriction in World War II the incidence of death from atherosclerosis was statistically reduced.

### Genetic Factors.

To the legion of contributors in the genetic field and those concerned with life assurance, it might seem ironical and anomalous that this avenue for consideration of atherosclerosis should be given such cursory attention. Whilst it has been established that patients with coronary artery disease do not necessarily have hypercholesterolæmia, there is a strong Mendelian trait in homozygotes and heterozygotes in xanthoma and hypercholesterolæmia respectively. In view of the high incidence of coronary atherosclerosis in subjects with these conditions, it is obvious that all relatively young people whose serum cholesterol level is elevated should be considered from the family background.

### Endocrine.

It has been postulated that testosterone stimulates connective tissue, and it is well recognized that coronary atheroma is more common in early adult life in the male than in the female human. Yet experimental work on the omnivorous bird and the herbivorous rabbit indicates that endocrine factors are at variance. Thus it has been shown that exogenous œstrogen in the case of cockerels and endogenous œstrogen at the physiological level in the laying hen prevent cholesterol-induced atherosclerosis, whereas no such suppression by œstrogen, exogenous or endogenous, occurs in the rabbit.

### Hæmodynamics.

It is thought by some that congenital anomalies of the coronary vascular tree may be a factor in the causation of atheroma. Paul Wood states that with left ventricular systole the blood in the deeper channels is pushed into the epicardial or surface vessels, which act as reservoirs. During diastole their elastic recoil along with aortic pressure pushes the blood back into the deeper vessels again. The suggestion, then, is that atheroma is found at bifurcation points because of the eddying that goes on.

### Enzyme Factors.

As might be expected, the field of cellular physiology is not without its proponents in the literature. It was found that free cholesterol was converted into cholesterol ester in greater percentage in normal than in atherosclerotic subjects, and so the possibility of a lipid enzyme such as cholesterol esterase has been given consideration as a preventive factor in atherosclerosis. Another group extracted a lyophilized powder from plasma heparin precursor and other tissue, such as rat and mouse pylorus, and found that the enzymatic properties of this preparation were identical with the lipæmia-clearing action of heparin injections. This avenue for therapy would appear most encouraging.

### Somatotype.

Many will recall in their medical experience the proneness of certain types to coronary occlusion—the mesomorphic, for example, as opposed to the ectomorphic somatotype. Studies have been carried out on criteria such as certain body measurements for the purpose of predicting this tendency. This phase of the subject is introduced for its possible implications in the investigation of the causes of coronary atheroma.

### Discussion.

Of the two theories advanced, the lipid-cholesterol theory offers infinitely more ground for search and speculation for a common denominator, and the *post hoc* and *propter hoc* position of cholesterol as a factor is rife in this regard. When nearly common ground is reached by one or more authorities, others, equally accredited, may take a tangential view. It would seem, however, that the original concept of cholesterol as the instigating agent is now on slender ground. At most it can be said that it is a frequent component of the atheroma under discussion; that its level in the serum is usually raised in people prone to coronary artery occlusion; that along with a fat-rich diet in certain individuals it may supply "the straw that breaks the camel's back"; and that when introduced into the system in the experimental animal it produces atherosclerotic lesions like those found in the human.

When allowance is made for the fact that coronary artery disease is found in people who are neither fat nor overweight, actuarial calculations based on necropsy studies of lipid and cholesterol deposits in the intima of arteries reveal that atheroma preponderates in overweight people and that the early deposits regress with weight reduction. At present opportunities for study in this direction are being used in the Korean war circle. The workers found a thickened intima in Korean soldiers, suggesting stress, but little atheroma, and it was proposed that the diet factor was needed as well to cause plaque formation. At the moment there seems little doubt that the lean and hungry societies or the "spare fat" diet people are better off in this regard. The Okinawans (oriental)

were found to be relatively free of cardio-vascular disease, hypertension and coronary occlusion not being found. These people were well proportioned and muscular, obesity was non-existent, and their diet was mainly carbohydrate, such as sweet potatoes, rice and vegetables; their protein intake consisted mainly of soya bean and infrequently meat and milk; their fat intake was very low.

Current views indicate that the extent of coronary syndromes is not necessarily a guide to the amount of coronary atheroma present. The degree to which this viewpoint is correct would appear to devolve upon the incidence of the intimal hæmorrhage, and the time would appear to be long overdue when the pathologist should settle this question for the clinician. Thus Paul Wood states that intimal hæmorrhage occurs in only 1% of cases of coronary occlusion; Wartman *et alii* gives the figure as 60%. Of prime significance is a recent study wherein cross-sections were made, with scrupulous technique, of the coronary arteries of 100 adults who had died suddenly of coronary artery disease, also of 75 controls. The findings were "hæmorrhages within atheromatous or fibrous plaques of the coronary arteries in almost all cases. The hæmorrhages are usually multiple and vary in age from fresh extravasations to areas of iron-containing pigmentation. All major branches are involved and the hæmorrhages are usually non-occlusive. Thrombi are frequently associated with older hæmorrhages, but not with fresh ones. Fresh mural hæmorrhages are not observed in the controls".

It is beyond comprehension that the English and American views quoted should be at such variance. The writer hopes that the former will prove substantially correct, since a vascular episode in an intimal plaque appears to provide in many instances the only anatomical, pathological and physiological concept for the clinical integration of varying anginal syndromes.

There would appear to be more than a suggestion that the lipid-cholesterol and thrombogenic (encrustation) theories are complementary. Recent work shows that a fat-rich meal increases the coagulability of the blood, thus favouring coronary occlusion in a predisposed person. Whilst it is neither the time nor place to enter into a problematical dissertation on the source and mode of action of heparin, the following aspects are relevant to what is about to be suggested: (*a*) It has been demonstrated that substances of a lipoid nature are concerned with blood coagulation. (*b*) Heparin retards the development of atherosclerosis in the experimental rabbit and reduces the number of large lipo-proteins of the $S_f$12-100 class in the serum of the atherosclerotic man, the circulating level of heparin being in inverse ratio to these large lipo-proteins. (*c*) Heparin affords relief in *angina pectoris* for periods of days. (*d*) It is thought that heparin is derived from the granules of mast cells (German authors), and these cells are found in the connective tissue of the walls of blood vessels where fat is being laid down.

Surely this triad of lipid, anticoagulant and atherosclerosis states a theme whereby the lipid-cholesterol and the thrombogenic hypotheses are reconcilable and consistent. The question is posed as to whether heparin is implicated through its influence on any thromboplastin issued into the plasma, owing to irritation from the atheroma plaque, its association with fat deposits in the walls of blood vessels, or its action on negative and positive ions ($\zeta$ potential).

The concept of atheroma resulting from the incorporation of a fibrinous deposit on the inner lining of the arterial wall and its subsequent hyaline and fatty change has jolted the long-accepted theory of intimal reactionary overgrowth. As was stated previously, this view is enhanced through the fact that a lipid factor is essential for blood coagulation. Briefly, is the story or mechanism thus: Mendelian trait → high fat and/or cholesterol intake → large lipo-protein molecule → blood-clotting factor → fibrinous deposit → intimal atheroma plaque?

When the complication of an intimal hæmorrhage is added in the case of a vascularized atheromatous plaque, it is suggested that there may accrue all the clinically acceptable possibilities as in the accompanying diagram (Figure I). It might be added here that Winternitz considered that the amount of cholesterol in the intima could be accounted for usually as the result of such hæmorrhage.

## SUMMARY.

1. The varying views of cholesterol as a factor in coronary atheroma with resultant occlusive disease have been explored and evaluated, and the manner of its entry and occurrence in the intima discussed.

2. It would seem from the evidence adduced that the fat in the various national diets is the determining agent rather than cholesterol, though the frequent association of raised serum cholesterol level with coronary disease is significant, and it appears necessary to restrict both fat and cholesterol intake in subjects predisposed to coronary heart disease.

3. Two seemingly opposed theories, one governing fat and lipid-cholesterol, the other fibrin deposit on the intimal lining, have been introduced.

4. It is postulated that these two theories are complementary, and that the unifying mechanism centres around the level of heparin in the circulating blood.

5. The validity of the claim for recognition of a century-old hypothesis points the fact that it is well to remember the past.

6. The need is implied for greater awareness of coronary atheroma as the background for the cardiac death on the certificate form.

## CONCLUSION.

The hope may be fulfilled in the not too distant future of a working concept for the control and management of coronary heart disease. The added life expectancy incidental thereto will involve the field of socio-economics with the impact especially referable to life assurance actuarial standards and related premiums. Surely it is a modest aspiration that early and appropriate research facilities will be instituted in the case of a disease that holds pride of place as the major item in the major cause of deaths in the western world.

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## CHEMICAL ADDITIONS TO FOOD AS FACTORS POSSIBLY CONTRIBUTING TO DISEASE.[1]

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My purpose in presenting this article is to draw attention to the toxic nature of certain chemicals commonly added to processed foods and to emphasize the dangers attending their use. I desire also to call attention to the current use of these processed foods in the modern economy and to a concurrent rise in the incidence of certain diseases which are known to be ætiologically associated with exposure to similar chemicals.

It is an accepted principle that food should be presented in an attractive form, because stimulation of the necessary digestive juices depends a great deal on the visual and olfactory senses. We have, from long experience, learned to associate certain colours with pleasant flavours, aromas or agreeable consistency, and colours thus play a very large part in our acceptance of foods. Butter would be unacceptable to most of us if coloured green, largely because we have been accustomed to butter being yellow, and similarly with other foods.

After a period of trial and error extending over many centuries, we have accepted certain natural foods as being non-injurious. This acceptance has not been without a certain amount of hazard over the years; but the fact that the human race has survived in the world is evidence that our process of trial and error has been reasonably successful. Over the last hundred years, however, we have been exposed to an additional hazard, the deliberate addition to natural foods of chemicals in the form of colourings, preservatives and flavours.

During the last half of the nineteenth century a great impetus was given to synthetic chemistry by the discovery of aniline dyes in 1856 by Perkins. This led to the synthesis of many new compounds, many of which, as far as we know, have never existed in Nature. A number of these new synthetic chemicals have been used in foods, and the cells of the body have therefore been exposed for the first time to the action of molecules to which in some cases they are vulnerable.

Living cells, although remarkably efficient in dealing with many noxious substances, are nevertheless often vulnerable to new molecules which may differ only slightly in chemical structure from biologically harmless substances —for example, methyl cholanthrene and the bile acid deoxycholic acid, the former a highly carcinogenic compound, the latter a constituent of a normal physiological secretion.

If I may be permitted to digress here, I would draw attention to the fact that methyl cholanthrene has been prepared from deoxycholic acid and cholesterol. In this connexion Barry *et alii* (1935) drew the following conclusions:

> Methyl cholanthrene thus establishes a clear connecting link between the carcinogenic hydrocarbons and the sterols and bile acids, and it is of great interest that the changes by which it is obtained from deoxycholic acid are all reactions of the type which are known to occur normally in the animal body, although there is no evidence that this particular sequence of changes involved in the formation of methyl cholanthrene does actually occur in Nature.

No evidence of the presence of even minute quantities of this substance has been found in either the cancerous tissue or the urine, but it is possible that such a substance acted as the initiating agent of the malignant change at an earlier stage. Cancerous growth is of such a nature that the process once begun will continue without further stimulation by the original irritating agent.

The living cell, then, can deal with certain naturally occurring noxious substances, and also, admittedly, with a number of synthetic products; but there are many of these latter products with which it cannot deal, and it is these that I now wish to discuss.

Aniline and many of its derivatives, the parent substances of many of the synthetic colourings, have been shown to induce nephritis, to form methæmoglobin with subsequent destruction of the red blood cells and also to induce agranulocytosis. Carcinogenic properties have also been attributed to aniline and some of its derivatives.

Beta-naphthylamine, an intermediate product in the manufacture of some of the azo dyes, has been shown to be a carcinogenic substance, as have also benzidine and a number of other aromatic amines. To the extent that they are methylated *in vivo*, it has been concluded by certain workers that the amino-azo dyes also are carcinogenic (Editorial, 1953). Two colourings that have been used in foods—Yellow AB and Yellow OB—are β-naphthylamines.

The naphthols also are toxic substances inducing nephritis and producing irritation of mucous membranes. Occasionally they have given rise to visual changes and partial retinal degeneration in man, and changes in the eye have been observed repeatedly in experiments on animals in which naphthol was absorbed. The retina is seen to be dotted over with bright points or to contain large yellow plaques. Atrophy of the optic nerve may follow (Cushny, 1947).

Sudan I, which is a benzene azo-β-naphthol, has been shown to produce hepatomata in mice (British Empire Cancer Campaign, 1948). Sudan III and Sudan IV, both azo-β-naphthols, when injected into the tissues, provoke an extraordinary growth of epithelium, which in some cases finally looks almost like a tumour. It is not clear how these substances act, nor what part is played by the injury they produce in the tissues; but the new growth is far in excess of what would be needed for repair.

Admittedly, in each of these cases a free amine would be produced on reduction of the dye; but I have seen no evidence that aniline, which would be one component in the reduction of Sudan I, causes hepatomata. On the other hand, Clayson (British Empire Cancer Campaign, 1952) has postulated that compounds which contain an ortho-aminophenol group and another ring system may be carcinogenic. The reason why some aromatic amines are carcinogenic whereas others have not been found to induce tumours, is that the former are more readily converted to ortho-aminophenol derivatives than the latter.

Some weight is given to this hypothesis by the fact that the carcinogenic metabolite formed from β-naphthylamine is 2-amino-1-naphthol. This substance has been shown to be carcinogenic by implantation of the chemical

[1] Read at a meeting of the Australian and New Zealand Association for the Advancement of Science, Canberra, January 13 to 20, 1954.

in the bladder, whereas the parent substance β-naphthylamine did not induce this reaction when implanted in the bladder (Clayson *et alii*, 1952).

In the case of some of the naphthol dyes, however, we have the ortho aminophenol with another ring system—the benzene ring—already to hand. We should therefore, while any doubt exists, prohibit the use of such dye substances as food colourings. Crocein Scarlet and Orange 11, both used as food colourings, are azo naphthols, and these are only two of a number of food colourings with this grouping.

That the sulphonic acid derivatives of some of these toxic groupings because of their solubility are non-toxic is a theory that has been held for many years. This theory, however, has recently suffered a serious challenge, since it has been demonstrated that Light Green SF, which is a sulphonic acid derivative of triphenylmethane, causes sarcoma at the site of injection in rats (Schiller, 1937). This finding immediately renders suspect Brilliant Blue FCF, Acid Green G, and Fast Green FCF, all sulphonic acid derivatives of triphenylmethane, having only minor differences in structure, and in fact these substances have recently been shown to produce fibrosarcomata in rats (Nelson and Hagen, 1953).

In this connexion it is interesting to recall that fuchsin, a triphenylmethane compound, was the dye considered to be responsible for the production of malignant tumours of the bladder in workers in dye factories in Germany. This was towards the close of the last century.

The German Research Commission appointed in 1949 to deal with the problem of foodstuff colouring matter considered that the water-soluble (sulphonated) azo dyes were safe for use in food provided that on reduction they gave sulphonated amines. Those from which free amines were produced were considered to be unsafe.

The finding in respect of free amines was based on the formation in the erythrocytes of Heinz inner bodies. It was found that in the case of those dyes from which free amines were produced, Heinz bodies were detected. Stewart H. Webster, in a summary to a review he made on the Heinz body phenomenon in erythrocytes (1949), made the following statement:

> These Heinz bodies, called by various names, appear to be newly formed particles originating either from the protoplasm or the membranes of the red blood cells in the course of irreversible injury by a toxic agent. The chemical nature of these particles is uncertain, but they appear to consist largely of denatured proteins. The presence in the blood of significant amounts of Heinz bodies is evidence of some injury to the erythrocytes. The indications are that some inorganic substances are capable of inducing this action as well as many aromatic nitro and amino compounds.

It is therefore not difficult to understand the attitude of the German Commission on this matter.

An interesting light is shed on the problem of the unsulphonated amine by the work of Gillman *et alii* (1949) with trypan blue. These workers found that injection of trypan blue produced reticulo-sarcoma in rat liver. This, however, was not the case with trypan red, a dye very similar in structure, which according to Gillman elicited none of the reactions produced by trypan blue.

A close examination of the structures of these two substances reveals that in the reductive cleavage of trypan blue at the azo linkages three substances would be formed, two only of which are sulphonated. The third would be a methylated benzidine (o-tolidine). In the case of trypan red, however, the reductive cleavage at the azo linkages would give three compounds, all of which are sulphonated.

In my opinion the reason for the carcinogenicity of trypan blue and not of trypan red is the formation in the body of o-tolidine, a free amine, in the reduction of trypan blue, whereas all amines formed on reduction of trypan red are sulphonated.

Methylation has been shown to increase carcinogenicity, and it has been suggested that this action is enhanced if the methyl groups are in the ortho position relative to the amino groups. For example, of the six isomers of aminoazotoluene fed by Crabtree to mice, only one—namely, 2'-amino-4:5'-azotoluene—failed to show any carcinogenic activity, and this is the only one of these which on reductive fission would not form an o-methyl amine. Furthermore, activity was highest in 4'-amino-2:3'-azotoluene which would divide to form two molecules, each containing an o-methyl amine (Walpole *et alii*, 1952). This work of Crabtree gives support to Clayson's suggestion, mentioned before, that simple o-hydroxyamines are direct acting carcinogens. On this hypothesis carcinogenicity would be expected in o-tolidine, as this compound is a dimethyl benzidine, the methyl groups of which are in the ortho position relative to the amino groups. Therefore to my mind it is not surprising to find that trypan blue shows marked carcinogenicity, as benzidine has been shown to be as dangerous a carcinogen as β-naphthylamine (Scott, 1952).

From these facts it follows that the sulphonated dyes would require close examination of their structures to determine the products likely to be formed on reduction, with a view to eliminating from food processing those which on reduction form free amines.

The colours that I have mentioned as examples are colours which are at present authorized for use in some or all of the States of the Commonwealth, and also in some cases in Great Britain, New Zealand and the United States of America.

Is there any relationship between chemical composition and carcinogenic activity? Many investigators have attempted to answer this question, but our knowledge is still largely empirical. We are, therefore, not in a position to say, merely by examining the chemical structure of a substance, that such a substance will possess carcinogenic properties. We can, however, suspect a substance because of the similarity of its molecule to that of a known carcinogen. A further difficulty is the fact that what may be a potent carcinogen for one species of animal may be quite innocuous for a different species.

It has been stated, in support of the use of food colourings containing or derived from toxic groupings, that many medicinal compounds contain or are derivatives of the same toxic molecules. Acetanilide, used in medicine, is a derivative of aniline, a toxic substance, and phenazone, another medicinal compound, is derived from phenylhydrazine, also a very toxic chemical. However, the contention that the use in medicine of compounds derived from or containing similar toxic groupings justifies the use in foods of colouring matter prepared from or containing similar groupings, cannot be sustained. Medicinal compounds in most instances are used for very short periods only; prolonged administration frequently produces toxic effects. Certainly, in the case of the two medicinal substances mentioned above, serious signs of toxicity will develop on prolonged administration.

The addition of chemicals to foods has increased considerably over the last hundred years, and has become in these days of processed foods an accepted procedure by manufacturers and consumers alike. However, many of these chemicals are now becoming suspect because of the similarity of their molecules to known toxic substances, or because of their proven toxicity.

I now wish to draw attention to the incidence of certain diseases, to demonstrate that the incidence follows very closely the increase in the use of chemical additives in foods. However, it is not my intention to give the impression that chemical additions to foods are wholly responsible for the increase in these diseases, but to indicate what I consider a possible contributing factor to a greater or lesser degree.

The leuchæmias are fatal diseases of unknown ætiology associated with gross disturbance of the leucopoietic tissues. Although it is usual to find pronounced leucocytosis, in some only slight increases are shown in the white cells, or even leucopenia. Sooner or later, however, according to the type of leuchæmia, immature and primitive white cells appear in the peripheral blood, while corresponding changes are to be found in the bone marrow.

In Australia the death rate from leuchæmia has risen from 1·8 per 100,000 in 1930 to 4·4 per 100,000 in 1950. Improved reporting would no doubt account for some, but not for all, of this increase.

Although leuchæmic conditions occur quite frequently in man, animals and birds, the ætiological problem still remains unsolved. Various theories have been propounded, of which the most commonly considered have been based on (*a*) infection, (*b*) neoplastic changes, (*c*) metabolic disorganization, (*d*) maturation defects in leucopoiesis due to deficiencies of specific factors, (*e*) toxic factors, (*f*) terminal changes in certain hæmatological diseases, and (*g*) familial and hereditary faults.

Dealing with toxic factors, Wilkinson (1951), writing in "The British Encyclopædia of Medical Practice", makes the following statement:

> It is well known that individuals who have been exposed to chronic benzene intoxications and many other chemical substances frequently develop leukæmic conditions. Further, it has been noted that there is definite evidence that the sulphonamide group of drugs in some patients has been responsible for the onset of acute leukæmia. In fact, there is quite a good deal of evidence to suggest that at least some leukæmias may arise from exposure to toxic factors. It may be that, directly or indirectly, whether at work, after therapy, or after ingestion of contaminated, adulterated or chemically treated foodstuffs, some of these factors, or other unidentified ones, may be responsible for the tremendous increase in leukæmia during the last 15 to 20 years.

Wilkinson goes on to state that in his series he has seen ten cases of acute leuchæmia that certainly linked up very closely with immediate prior treatment, with one or other of the sulphonamide derivatives, for colds or other infections. This should sound a note of warning against the indiscriminate use of the sulphonamides. Incidentally, sulphanilamide, the parent substance of these compounds, has been widely used as an intermediate in the dye industry.

J. and O. Furth (1938) succeeded in producing experimental leuchæmia in mice by inoculations with benzpyrene, a highly carcinogenic substance, thus showing that this condition may be artificially produced by means of a carcinogenic substance.

Could there not be some connexion, then, between the increased use of chemicals in foods and the increase in the incidence of the leuchæmias? We know that certain substances, such as the sulphonamides, can induce agranulocytosis, and Wilkinson has shown the apparently close link between acute leuchæmia and treatment with sulphonamides. Is it not, then, reasonable to assume that the same agent in a certain dosage will cause inhibition or destruction, and in another smaller continued dosage (such as would obtain by the ingestion of foods with added toxic chemicals) cause irritation of the cells, with subsequent uncontrolled stimulation of the cell mechanism and the production of immature and primitive cells such as are found in leuchæmia?

A number of dye substances used as colouring for foods are derived from, or have as a component, aniline, a substance known to induce agranulocytosis. Induline, nigrosine and azogeranine are food colourings which fall within this category.

Let us now examine the position in regard to cancer. No one can dispute the increase in cancer in the last century. In the United Kingdom, for example, from 1851 to 1950 the death rate per 100,000 of the population has risen from 29·01 to 188·09. Statistics for Australia are available only from 1908, but these figures also show an increase per 100,000 from 68·32 in 1908 to 125·94 in 1951. Here again, improved reporting would account for some but not for all of this increase.

The direct correlation between this increase in cancer and the aging of the present-day population cannot be denied; but in the absence of any other supporting evidence to regard complacently these two coincidental factors as standing in the relationship of effect and cause is unscientific and may be wilful self-deception.

I consider it would be more logical to infer that more of the population are becoming victims of cancer because of the increased period of exposure to the effect of carcinogenic influences, which to be effective require long-continued application to, or ingestion by, the body. The long latent period that may be involved between the first exposure to a carcinogen and the development of recognizable disease has been demonstrated in the case of workers with β-naphthylamine, among whom the period was on the average 15·5 years with a range from seven to twenty-two years (Scott, 1952).

The ætiological problem of cancer also remains unsolved. Various theories have been advanced, and among those considered is that based on the persistent injury to the cell by chemical substances. In considering the theory of persistent injury to the cell by chemical substances, I feel that there is no doubt that certain evidence points to the chemical irritant agency introduced into the body as at least a contributing factor in neoplastic disease. As was pointed out before, long-continued exposure to even small quantities of toxic substances ultimately produces recognizable cancer.

That our knowledge of the carcinogenic nature of many chemical substances comes largely from our experimentation on rats, mice, dogs and other animals cannot be denied. Nor can it be denied that the human body may not react in the same manner; but surely if any doubt exists it is far better to err on the side of safety.

To sum up then, it has been demonstrated by a number of investigators that cancer and the leuchæmias follow the application or ingestion of various chemical substances. As a number of additives used in food processing are derived from or contain these proven toxic chemicals, it behoves us to take steps to remove these from our foods. I feel we have sufficient evidence to assume that some at least are contributing factors, if not something more, in the increase in the diseases I have discussed.

The questions, then, that must be answered for each additive used in processing food are the following: (*a*) Is the additive itself a toxic substance? (*b*) Is the additive containing one or more toxic groupings toxic in the final form produced? (*c*) If it is not apparently toxic in the final form produced, is there a possibility of its dissociation in the body to form toxic products? (*d*) Is any toxic substance an intermediate product in the manufacture of the additive and therefore possibly present in the final product as an impurity?

It would appear that substances produced from aniline, phenylhydrazine, naphthols, naphthylamines and triphenylmethane or any substance from which any of these chemicals are produced as intermediates should be suspect.

As an alternative to synthetic chemicals at present in use for food colourings, for example, could we not use some of the naturally occurring pigments of plants? Natural colourings belong mainly to few groups of chemical substances. These include porphyrins, such as the chlorophylls and hæmoglobin; pyrone derivatives, notably flavones and anthocyanins; polyenes, such as the carotenoids; a few complex quinones and some phenolic acids such as the tannins. There are a few others, but generally it will be noticed that nitrogen plays only a minor part; nitro derivatives, azo compounds and triphenylmethane derivatives such as we find in the synthetic dyes are conspicuous by their absence from naturally occurring colours.

A number of these colourings, such as the flavines, carotenoids and xanthophylls, are of dietetic value because of their association with the known essential vitamins or with known biological activities.

Speaking on the subject of the dietetic aspects of colours in food the late H. E. Cox (1944) had this to say:

> The colours in food are not merely for æsthetic purposes; indeed, just as in some animals and plants colour is for protection, for camouflage, or for sexual purposes, so in food it seems that the colours have definite physiological values and attributes which we are only now beginning to realize or understand. It seems to me that the time has come or at least is approaching when it is pertinent to ask if the types of dyes which are being

used are the best for the purpose. They may well be the best from a purely tinctorial point of view; they may be those which are relatively cheap or can be produced with ease; but are they the best from a dietetic or physiological standpoint? Should not the fact that Nature uses a carotenoid, an anthocyanin or a xanthophyll suggest that it may be desirable to use these natural colourings in processed foods?

At first sight this would appear to be the solution to the problem of colouring foodstuffs. However, closer examination reveals a number of difficulties. The majority of the natural pigments are sensitive to one or more of a number of conditions and generally are somewhat reactive. This instability would preclude their use in most processed foods. The carotenoids, for example, are polyene pigments consisting wholly or chiefly of long acyclic chains of carbon atoms united in an uninterrupted sequence of double bonds. Because of this unsaturation these polyene pigments are somewhat reactive. The shorter chain compounds are yellow in colour. To obtain deeper colours it is necessary to increase the number of unsaturated carbons in the chain. By so doing we increase the reactivity of the compound. As stability is a prerequisite for food colourings, the outlook for this group is not promising, and indeed this reactivity and sensitivity appear to be common to most of the naturally occurring pigments.

Certain quinone pigments have been synthesized, but unfortunately these have undesirable physiological reactions. Some initial work has also been done on the synthesis of compounds having a similar molecular arrangement to chlorophyll, but having different groupings from those found in this natural pigment. However, these syntheses would indicate that more research may be productive of results which could give us colouring matter free from the undesirable effects of some synthetic coal tar derivatives at present being used.

We should, therefore, reexamine our food legislation with a view to banning the addition to food of synthetic substances containing known toxic groupings. This seems to me to be the safest procedure at present, in view of the alarming increase in the diseases I have mentioned. The deliberate addition to food of chemical substances with known toxic groupings constitutes a risk which should be avoided. Rather we should explore the possibility of the use of naturally occurring substances or develop the synthetic production of substances the structures of which closely resemble those found in Nature, or which possess structures differing from those at present suspect. Furthermore, definite standards of purity and composition should be established for those which are approved for use in foodstuffs.

### Summary.

1. Attention is drawn to the toxic nature of certain chemicals commonly added to processed food.

2. The increase in certain diseases and the increased use of chemicals in foods and the possible relationship of both are discussed.

3. The suggestion is made that food legislation should be examined with a view to banning the addition to foods of certain synthetic chemicals.

4. A plea is made for further research into the use, as food colouring, of natural pigments, of colours produced synthetically from groupings similar to those found in natural pigments, or from groupings differing from those at present suspect.

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## Reports of Cases.

### THE STUDY OF ELECTROLYTE AND WATER BALANCE IN A CASE OF PINK DISEASE.

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IN a recent and detailed review concerning our present understanding of pink disease (Cheek, 1953*b*), the coexisting disturbance of water and electrolyte metabolism was emphasized. Attention was directed to the possibility that such a disturbance might be causally related to many of the symptoms and signs of this condition. Except for the work of Warkany and Hubbard (1948, 1951) and of Fanconi and his associates (1948), little proof is available to support any ætiological factor. This paper does not throw any further light on the rôle of mercury, but it attempts to expose the nature of the existing disturbance of water and electrolyte metabolism.

The case to be presented is a mild example in a girl, aged five years. The study of the disease in an older child was fortunate in that the accurate collection of specimens became an easier problem.

#### Clinical Record and Pertinent Findings on Examination.

For the past three months X. had been unable to stand properly. She was lethargic and frequently in a state of fatigue. She complained of pain in her feet, hands and legs. Weight loss had been most noticeable and her appetite had been poor from the onset of her illness. The mother stated that her child had altered psychologically and that irritability had been remarkable. She regarded her as a "nervous child". Her hair had been falling out and sweating was particularly noticeable. She was constipated and seemed to be passing urine frequently. Five months prior to her admission to hospital she had been treated with hexyl-resorcinol and "powders" for a worm infestation. Since the development of these symptoms

[1] This work was assisted by Tuberculosis Control Funds, allocated by the Province of Ontario from National Health Grants. Some of the data from this case were presented before the Royal College of Physicians and Surgeons, Montreal, October 30, 1953.

several doctors had been consulted and the diagnosis had ranged from rheumatic fever, chronic tonsillitis, rheumatoid arthritis and hypothyroidism, to "the nervous child".

On examination, hypotonia was extreme; sweating was noticeable; the hands were cold, but only slightly pink. Peeling was observed between the fingers. The pulse rate was 160 per minute and the blood pressure registered 120 millimetres of mercury, systolic, and 90 millimetres, diastolic. Alopecia was present on the crown of the head (Figure I), and the teeth were loose. One tooth subsequently was lifted from its socket. The clothes and bed linen were wet with sweat.

The child was placed on a fifteen-day balance study and her diet changed to orange juice and whole milk. (Approximately, two parts of orange juice to one part of milk were the proportions of each taken. The caloric value of both milk and orange juice with sugar was in the region of 730 calories per litre.)

FIGURE I.

## Methods.

The measurements of extracellular water and total body chloride content were carried out by the use of sodium bromide (Cheek, 1953*a*). The total body water content was measured by the method of Soberman *et alii* (1949). Sodium and potassium analyses were carried out with the aid of an internal standard flame photometer (Perkin Elmer), and chloride was determined by the method of Schales and Schales (1941). Serum bicarbonate content was estimated by the method of Van Slyke and Neill (1924). For serum and urine creatinine contents the method of Hare (1950) was employed. Carbon or carmine markers were given to define the stool losses for the different periods. The food or fluid intake was duplicated and an aliquot of this was taken for analysis. All estimations of intake and of urine and stool excretion were made in duplicate.

TABLE I.
*Period 1.*

| Day. | Weight. Kilograms at 7 a.m. | Fluid Intake. (Millilitres.) | Urine Output. (Millilitres.) | Sweat *plus* Insensible Water Loss as a Percentage of Fluid Intake. | Urine Balance (Milliequivalents). | | | | Total Chloride. (Milliequivalents). | Extracellular Water. (Millilitres.) | Serum Electrolytes (Milliequivalents). | | | | | | Therapy. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Sodium. | Potassium. | Chloride. | Nitrogen. (Grammes.) | | | Sodium. | Potassium. | Chloride. | Carbon Dioxide. | pH. | Non-Protein Nitrogen. | |
| 1 | 14·4 | 1940 | 920 | 53 | 8·30 | 4·80 | −2·10 | — | 375 | 3150 | 136 | 4·2 | 94·0 | 27·3 | 7·50 | 34 | — |
| 2 | 14·2 | 2750 | 740 | 73 | 19·84 | 22·28 | 20·64 | — | — | — | — | — | — | — | — | — | — |
| 3 | 14·4 | 2900 | 1000 | 62 | 18·74 | 32·70 | 27·20 | — | — | — | — | — | — | — | — | — | — |
| 4 | 14·5 | 2380 | 1140 | 52 | 13·30 | 16·60 | 19·60 | — | — | — | — | — | — | — | — | — | — |
| 5 | 14·5 | 1000 | 530 | 47 | −5·05 | −6·30 | 2·77 | — | — | — | 133 | 5·0 | 102 | 24·5 | 7·42 | 25 | Potassium chloride. |
| 6 | 14·3 | 1140 | 255 | 78 | 0·00 | 1·60 | 8·70 | — | — | — | — | — | — | — | — | — | Potassium chloride. |
| 7 | 14·1 | 2200 | 720 | 67 | 11·66 | 15·68 | 24·96 | — | — | — | — | — | — | — | — | — | Potassium chloride. |
| 8 | 14·1 | 2620 | 1820 | 50 | 9·10 | 6·20 | 13·80 | — | 475 | 3850 | 139 | 5·2 | 97·7 | 24·3 | 7·39 | 33 | Potassium chloride. |
| Total retention .. .. .. | | | | | +75·85 | +93·54 | +115·67 | — | +100 | +700 | — | — | — | — | — | — | — |
| Correcting for stool loss .. .. | | | | | +75·0 | +64·5 | +114·0 | — | — | — | — | — | — | — | — | — | — |
| Correcting for nitrogen retention .. | | | | | +75·0 | +60·0 | +114·0 | +1·67 | — | — | — | — | — | — | — | — | — |

## Results.

In Table I the results of the balance studies are recorded together with other electrolyte investigations. The first eight days were taken as the initial period, and the next seven days as the second period. The serum electrolyte values are placed so as to correspond with their respective periods. During the last four days of the first period two grammes of potassium chloride were added to the fluids offered. However, on the fifth and sixth days the fluid and electrolyte intake was low, by comparison with the other days.

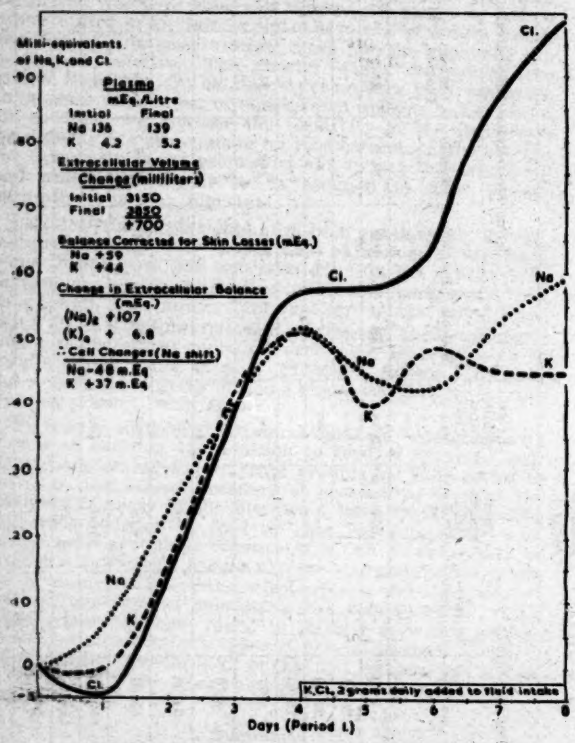


FIGURE II.

Cumulative electrolyte balance (corrected for skin losses) for eight days from a five year old child, weighing 14·4 kilograms, with pink disease. The balance data have been corrected for losses from the skin and lungs, but not for sweat losses. The resulting retentions are significantly high for all three ions. By calculation on the basis of the bromide space, changes of cell electrolytes are demonstrated (vide data on left hand side). If the amounts of electrolyte lost in the sweat under usual circumstances are borne in mind, these retentions over this period remain significant.

*Estimation of the serum electrolytes on the first day* revealed the presence of metabolic alkalosis. The total body chloride content was 375 milliequivalents, or 25 milliequivalents per kilogram, a 30% reduction when compared with the normal child of the same weight (Cheek, 1954*a*, in the press). The extracellular water (or bromide space) was diminished to a similar extent. This value has been corrected by 10% for the entry of bromide into red cells (Cheek, 1953*a*). The total body water content was only 45·7% of the body weight, which would also represent a reduction in the region of 30%.

The glomerular filtration rate as measured by the endogenous creatinine excretion was low (53·7 millilitres per square metre per minute). During days one to four appreciable amounts of sodium, potassium and chloride were retained. This was possibly related to the imposition of a diet rich in electrolyte (orange juice). Enough

TABLE II.
*Period 2.*

| Day. | Weight. (Kilograms at 7 a.m.) | Fluid Intake. (Millilitres.) | Urine Output. (Millilitres.) | Sweat plus Insensible Water Loss as a Percentage of Fluid Intake. | Urine Balance (Milliequivalents). | | | | Serum Electrolytes (Milliequivalents). | | | | | | Therapy. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Sodium. | Potassium. | Chlor de. | Nitrogen. (Grammes.) | Sodium. | Potassium. | Chloride. | Carbon Dioxide. | pH. | Non-Protein Nitrogen. | |
| 9 | 14·4 | 3360 | 2230 | 32 | +6·80 | +5·90 | −0·60 | — | 139 | 5·2 | 97·7 | 24·3 | 7·39 | 33 | Potassium chloride D.C.A. |
| 10 | 14·7 | 3180 | 2040 | 36 | −1·12 | −2·90 | +17·90 | — | — | — | — | — | — | — | Potassium chloride D.C.A. |
| 11 | 14·8 | 2920 | 1930 | 56 | −4·89 | +22·60 | +12·10 | — | — | — | — | — | — | — | Potassium chloride D.C.A. |
| 12 | 14·8 | 2720 | 1590 | 61 | +4·91 | +25·90 | +18·10 | — | — | — | — | — | — | — | Potassium chloride D.C.A. |
| 13 | 14·4 | 2340 | 1240 | 47 | +2·22 | +5·90 | +11·10 | — | — | — | — | — | — | — | Potassium chloride. |
| 14 | 14·5 | 2650 | 1480 | 44 | +1·80 | −3·90 | +6·00 | — | — | — | — | — | — | — | Potassium chloride. |
| 15 | 14·4 | 1960 | 1280 | 35 | −4·40 | −8·10 | −2·70 | — | 142 | 5·4 | 109 | 23·7 | 7·45 | 37 | Potassium chloride. |
| Total retentions | .. | .. | .. | .. | +4·90 | +44·70 | +56·90 | — | — | — | — | — | — | — | — |
| Correcting for stool loss | .. | .. | .. | .. | +4·0 | +19·0 | +55·0 | — | — | — | — | — | — | — | — |
| Correcting for nitrogen retention | .. | .. | .. | .. | +4·0 | +15·0 | +55·0 | +1·81 | — | — | — | — | — | — | — |

potassium was retained to neutralize the alkalosis. The serum pH and bicarbonate level were within normal limits at the end of the fourth day. The serum sodium concentration at that time was significantly low.

By the end of the first period, 75 milliequivalents of sodium, 60 milliequivalents of potassium and 114 milliequivalents of chloride had, according to the balance data, been retained. However, the total body chloride content as measured by bromide was 475 milliequivalents, and the extracellular water was 3850 millilitres (a gain of 700 millilitres). The total chloride content had increased 100 milliequivalents.

The results obtained by balance study do not account for electrolyte losses that normally occur through the lungs and skin, nor do they define the electrolyte losses occasioned by sweat secretion. With respect to the first correction, this amount would not exceed two milliequivalents of sodium, potassium or chloride per day (Darrow, personal communication). In Table III this correction has been made and the resulting balance is recorded.

Calculating on the basis of the extracellular position of chloride (or bromide) by the method of Darrow (*vide* Gamble, 1951, for detailed explanation), we can deduce that during the first period there was an increase of 107 milliequivalents of extracellular sodium and 6·8 milliequivalents of extracellular potassium. If the balance for period 1 in Table III is taken into account, the data predict that 37 milliequivalents of potassium entered the tissue cells and 48 milliequivalents of sodium returned to the extracellular fluid. The data obtained have been conveniently represented in Figure II.

It is clear that during the first period, in terms of milliequivalents per kilogram, seven of chloride, four of sodium and three of potassium were retained. These amounts are significant, but we have made no mention of sweat losses. The concentration of potassium in actual sweat is likely to be between 10 and 15 milliequivalents per litre of sweat, while sodium and chloride concentration may be as low as 10 or as high as 50 milliequivalents per litre. The losses of sodium and chloride in sweat are normally equivalent (Darrow and Pratt, 1951). If we take into consideration the losses of electrolyte which can occur in the sweat under normal circumstances, then the overall balances are still too great by at least two milliequivalents per kilogram.

During period 2, two grammes of potassium chloride were added to the fluid intake. For the first four days of this period (Table II) desoxycorticosterone acetate was given in a dosage of two milligrammes by intramuscular injection. It is of interest to note that no appreciable sodium retention occurred as a result of the administration of this steroid. If one accepts the balance data, there was, during this second period, a retention pattern of *plus* four milliequivalents of sodium, *plus* 15 milliequivalents of potassium and *plus* 55 milliequivalents of chloride. If we allow the same correction of two milliequivalents for lung and skin losses (excluding sweat), we shall obtain results as shown in Table III. The balances of sodium and potassium suggest a restoration of tissue composition, but the positive balance for chloride is large and is difficult to explain. During normal growth, greater amounts of sodium than chloride are retained.

At this time the glomerular filtration rate showed a rise to 125 millilitres per square metre per minute. In Table I and Table II it will be further noticed that during the second period the fluid intake improved; the volume of sweat and insensible water (expressed as a percentage of the fluid intake) tended to decrease.

During periods 1 and 2, two twenty-four hour specimens of urine were assayed for mercury. The excretion was found to be *nil*. (The normal excretion is below 0·05 milligramme of mercury per day.) After periods 1 and 2, one gramme of sodium chloride was also added to the diet, and 12 injections of BAL (British Anti-Lewisite) were given (three milligrammes per kilogram per day). As a result of this treatment, 0·16 milligramme of mercury was excreted per day.

The 17-ketosteroid excretions (expressed as androsterone) during periods 1 and 2 were 2·21 and 2·18 milligrammes respectively. This is the excretion for a ten-year-old child, if one accepts the levels taken by this hospital. The corresponding urinary excretions of 11-oxysteroid were 0·34 and 0·29 milligramme respectively. The normal value accepted at The Hospital for Sick Children is 0·05 to 0·3 milligramme per day.

Improvement in the clinical condition dated from the end of the first week in hospital, and by the twenty-sixth day the child weighed 15·2 kilograms; the blood pressure had fallen to 110 millimetres of mercury, systolic, and 70 millimetres, diastolic. Except for the alopecia, which was giving place to a growth of new hair, one would probably not have known the previous diagnosis. Sweating was no longer detected, and one gramme of potassium chloride was the only addition to the diet. The urine volume now accounted for 60% of the fluid intake.

TABLE III.

*Balance Studies: Corrections for Skin Loss Without Accounting for Sweat Loss.*

| Balance. | Milliequivalents of | | |
|---|---|---|---|
| | Sodium. | Potassium. | Chloride. |
| *Period 1* | +75 | +60 | +114 |
| Allow 2 milliequivalents loss from the skin per day for sodium potassium and chloride | −16 | −16 | −16 |
| Corrected balance | +59 | +44 | +98 |
| *Period 2* | +4 | +15 | +55 |
| Allow 2 milliequivalents loss from the skin per day for sodium, potassium and chloride | −14 | −14 | −14 |
| Corrected balance | −10 | +1 | +41 |

On the twenty-eighth day the total body chloride content had risen to normal for weight (560 milliequivalents, or 37·5 milliequivalents per kilogram). The 17-ketosteroid excretion was normal, and likewise the blood pressure. The serum electrolytes expressed in milliequivalents were as follows: sodium, 144; potassium, 4·75; chloride, 103; carbon dioxide, 24·3. The serum pH was 7·42. The child was discharged on the thirty-second hospital day. Her weight was then 16 kilograms.

### Discussion.

Children with pink disease have a low serum chloride concentration, which may also be associated with a reduction of the serum sodium concentration. The serum bicarbonate level may be significantly high, and metabolic alkalosis with a rise in serum pH is to be expected. We know that metabolic alkalosis is characteristic of cell potassium deficiency (Darrow, 1945, 1946, 1948). Under these circumstances both sodium and hydrogen ion replace losses of cell potassium (Cooke, Segar, Cheek, Coville and Darrow, 1952; Orloff, Kennedy and Berliner, 1953).

The measurement of total body chloride content, which is also an index of extracellular water, was significantly low and showed an appreciable increase with electrolyte therapy. Elsewhere (Cheek, 1954*a*) 50 normal infants and children have been studied with respect to total body chloride content. Stable bromide has been used for this purpose, since the volumes of distribution of chloride and bromide differ by only 2% (Gamble, 1953). By comparison with normal children, in the case reported above a 30% reduction in total body chloride content was revealed. By contrast, I have found in children in states of poor nutrition an expansion of extracellular water content and an increase in total body chloride content (Cheek, 1954*b*, in the press). Starvation leads to a decrease in intra-

cellular water and to a loss of body fat. Expansion of extracellular water usually results. The significance of a low total chloride content in pink disease is further enhanced when we give consideration to these facts.

It must be emphasized that the serum chloride concentration is not necessarily an index to the status of total body chloride (Cheek, 1954*b*, in the press). This fact has possibly in the past obscured our appreciation of the changes in electrolyte balance in this condition.

The loss of extracellular water and of total body water in the present case measures the extent of dehydration. Similar findings have been previously obtained. Hypotonic dehydration favours a relative increase in cell hydration (Darrow and Yannet, 1935).

In the first eight-day period of this study there was a reexpansion of extracellular water as a result of potassium chloride therapy. Since there was no increase in body weight over this period, it must be concluded that this return to normal extracellular hydration was at the expense of cell water.

In one previous case a 30% reduction of plasma volume was found (Cheek, 1953*b*). The reduction of total body water, of chloride and of extracellular water is here of the order of 30%.

The glomerular filtration rate in the present case (patient X.), as defined by endogenous creatinine excretion, was found to be low. This adjustment reduces the chloride load delivered to the kidney tubules and, therefore, effects a conservation of this ion by virtue of a greater economy in tubular reabsorption.

These findings therefore predict that there are deficits of cell potassium, of chloride and of extracellular sodium and water. Balance studies have confirmed that this is the case. The retention of these ions during period 1 was greater than would normally be expected. Potassium is retained and more chloride than sodium is retained. This latter phenomenon indicates that sodium must come from the cells, for we believe that chloride remains chiefly extracellular.

In pink disease we are faced with two possible avenues of chloride loss. Firstly, one must consider the kidney. This is the master organ of homœostasis. The simultaneous occurrence of a urinary chloride loss together with measured deficits of total body chloride would seem significant. On the surface this would suggest that there was a failure of proper reabsorption of chloride in the kidney tubules. Such an event is produced by mercurial diuretics, and this can lead to metabolic alkalosis, cell potassium loss, dehydration, and a reduction of glomerular filtration (Schwartz and Wallace, 1951). We know that mercury has been incriminated as an ætiological factor in this disease (Warkany, 1951). However, a large continuous and concomitant chloride loss in the sweat could account for all these findings.

In period 2, the balance study revealed an overall retention of chloride. During other observations one has noticed that the retention pattern indicated a larger absorption for chloride than for sodium or potassium. Under normal circumstances the growth of a child ensures a small, but slightly higher, retention of sodium than of chloride. In fact, a greater relative absorption of chloride can be explained only on the grounds that a gross disturbance of body composition has previously existed (Darrow, personal communication).

We are aware of the inherent errors in balance technique, and the large overall retention of chloride in period 2 may have been due to an error in technique. In period 1 the measurement of total chloride content agreed reasonably well with the expected retention of chloride demonstrated by balance study. Another recent case (Cheek, 1954*b*, in the press) has shown almost identical findings with that of period 1 in the present case.

It remains to be shown whether the increase of venous pressure (Cheek, 1953*b*), arteriolar spasm (as predicted by Vulliamy, 1953), and the elevation of blood pressure are related to electrolyte imbalance. Hypotonia is likely to be related to the changes in muscle cell composition.

It was originally shown by Cheek, Hetzel and Hine (1951) that the excretion of 17-ketosteroids is significantly high in pink disease. In this case and in two other recent cases a high 17-ketosteroid excretion has been found. This finding is of great interest, as it is known that under circumstances of malnutrition the 17-ketosteroid excretion tends to be significantly low (Landau *et alii*, 1948). Since the urinary excretion of 11-oxysteroid is normal (Cheek, Hetzel and Hine, 1951; Bornstein and Trewhella, 1951), it may be that excessive amounts of 11-oxysteroid are lost through the sweat (Nichols and Miller, 1948). The evidence supports the belief that there is increased activity of adrenal function. This phenomenon may represent an unsuccessful attempt to conserve sweat electrolyte loss (Conn, 1948).

These investigations support the belief that children suffering from pink disease should receive additional electrolyte in their food or fluid intake. Orange juice is a rich source of potassium. However, further work is necessary before we can obtain a clear picture of the electrolyte disturbance and of the exact magnitude of these deficits.

Because the greatest water expenditure is in the form of sweat and insensible water loss, only 30% or less of the fluid intake may be available for excretion as urine. This is of importance. In the early stages, forced feeding with foods high in nitrogen content, without adequate glucose and water, will provide a large solute load which in all probability the kidney is unable to excrete effectively. This will produce a further deterioration of hydration. This danger has been demonstrated in normal infants who are not even subject to excessive sweat loss (Pratt and Snyderman, 1953). Cognizance must be taken of the protein-sparing effect exerted by glucose (Gamble, 1951). Three grammes of glucose per kilogram not only produce an antiketogenic effect, but diminish losses of protein in the fasting patient. Moreover, glucose will reduce the solute load on the kidney and will thus economize on water and electrolyte expenditure.


### Summary.

A patient suffering from pink disease has been subjected to a fifteen day electrolyte balance study. The measurements of total body chloride content and total body water content have been carried out. Steroid excretion and glomerular filtration have been investigated.


### Conclusions.

1. Metabolic alkalosis is associated with a 30% reduction of total body chloride and of extracellular water. Total body water is reduced to a comparable extent. Glomerular filtration is less than normal.

2. During the first eight days of this study significant amounts of potassium, chloride and sodium were retained.

3. Extracellular sodium probably replaces lost cell potassium.

4. The reason for this disturbance of electrolyte balance has not been elucidated. Attention has been directed to the study of sweat and electrolyte losses, and to kidney function.


### Acknowledgements.

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# Reviews.

**Parsons' Diseases of the Eye.** By Stewart Duke-Elder, K.C.V.O., Ph.D., D.Sc., LL.D., M.D., F.R.C.S., F.A.C.S.; Twelfth Edition; 1954. London: J. and A. Churchill, Limited. 8½" × 5½", pp. 614, with 22 plates in colour and 465 text figures. Price: 42s.

AFTER an interval of some six years a new edition of "Parsons' Diseases of the Eye" has appeared, similar in size and binding to previous editions, but now written, or issued, under the name of Sir Stewart Duke-Elder.

The author states that few changes have been required in the chapters dealing with anatomy and optics, but that most of the text has been rewritten in regard to etiology and pathology, especially those associated with virus diseases, the ætiology of uveitis, retinopathies, glaucoma and other manifestations of general disease. It has been the policy to avoid overloading a book intended primarily for students and general practitioners.

This edition is of 606 pages. The eleventh had 740. There are 22 coloured plates and 465 text-figures. All the former are new, and many of them, especially those relating to the *fundus oculi*, suffer by comparison with those of the eleventh edition (most of which were from the master-hand of A. W. Head). The black and white photographic reproductions, and many of the drawings, are not an improvement. On the whole, the illustrations are not as good as they could, or should, be. Another regrettable feature is the absence of a key to the coloured plates in the page of contents.

A very valuable reference—"Requirements of Candidates for Admission to the Public Services" (*Appendix 3 of the* eleventh edition) has been omitted, and surely could have been retained, even at the expense of its 14 pages.

The book is brimful with excellent text and subject matter and is far too large for undergraduate needs; it could be valuable for the general practitioner who possesses some working knowledge of ophthalmology, and especially for the resident medical officer and the graduate proceeding to a diploma.

The chapter on general therapeutics is as up to date as any such non-static subject can be—chemotherapy, antibiotics, the hormones, cortisone and ACTH being included.

"Parsons'" has been an excellent book, from the first edition (1907), and this twelfth edition merits very high commendation, even though it may not measure up to all the demands and expectations of the illustrations.

**Ciba Foundation Colloquia on Endocrinology: Volume VII: Synthesis and Metabolism of Adrenocortical Steroids.** *Consulting Editor for this volume*, W. Klyne, M.A., B.Sc., Ph.D.; Editors for the Ciba Foundation, G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S.; 1953. London: J. and A. Churchill, Limited. 8" × 5½", pp. 316, with 875 structural formulæ and 29 illustrations. Price: 30s.

A SERIES of colloquia have been held under the ægis of the Ciba Foundation on steroids at which experts from Europe and America discussed recent advances in research on steroids. The latest volume, *Volume VII, deals* with the synthesis and metabolism of adrenocortical steroids. There are 12 papers on synthesis of adrenocortical and related steroids each with discussion, and eight papers on metabolism of adrenocortical steroids. The papers are all by workers of the highest standard in the field. To follow the papers on the synthesis of the steroids one must have a considerable knowledge of this branch of organic chemistry, and few medical men have the necessary knowledge. The papers on the metabolism of the steroids make very difficult reading even to a biochemist who has followed recent work, but one must be impressed by the evidence of the amazingly rapid advance in our knowledge during the past few years.

This is the most difficult of the volumes so far published, but anyone who has followed recent work on cortisone and allied steroids cannot fail to find much of interest in it.

**Clinical Electrocardiography.** By David Scherf, M.D., F.A.C.P., and Linn J. Boyd, M.D., F.A.C.P.; Fourth Revised Edition; 1953. London: William Heinemann (Medical Books), Limited. 8¾" × 5½", pp. 508, with 292 illustrations. Price: £2 2s.

THERE will always be a place in a general practitioner's library for a text on electrocardiography which is profusely illustrated, easy to read, with a good index, and above all containing clinical correlations between the tracings and the bedside situation. D. Scherf and L. J. Boyd's "Clinical Electrocardiography" has all these attractions and can be confidently recommended to all possessors of electrocardiographs. The deplorable American practice of selling an electrocardiograph and an atlas of electrocardiograms together has fortunately, as far as we know, not spread to this country, but, if it does, the agent would transgress less if the atlas was replaced by "Scherf and Boyd".

The fourth edition is enlarged by further description of the unipolar leads, vector-cardiography, the œsophageal electrocardiograms, preexcitation syndrome *et cetera*. There is not a great deal of prolonged physical or algebraic orientation, but there are frequent references instead to clinical findings and even to therapy.

The authors have consistently defended "empiricism" in cardiography, so that they have not entered into long hypothetical interpretations and not much of the text has had to be changed with the changing concepts. Thus there is little to be said about the electrodynamics of cardiac infarction. The electrocardiography of congenital heart disease is distinctly curtailed and some of the statements and explanations are frankly provocative. The sections on arrhythmias, heartblock, exercise tests and effects of electrolyte disturbances on the tracing are some of the best.

There are nearly three hundred illustrations in over 450 pages. Most of these are of the standard leads only and some are rather faint and the intended lessons blurred. Happily the legends are short, the paper is good and the paragraphs are short. Some of the authors' special interests are revealed by obsolete discussions on the terminology of bundle branch block, extrasystoles, and so on; but in the main the book is well balanced, well indexed and well worth the price. The bibliographies at the end of each chapter are of special interest for seekers of original articles in German.

**The Quest for Youth: A Study of All Available Methods of Rejuvenation and of Retaining Physical and Mental Vigour in Old Age.** By George Ryley Scott, F.Ph.S. (Eng.), F.Z.S., F.R.A.I.; 1953. London: Torchstream Books. 8¼" x 5½", pp. 158. Price: 10s. 6d.

THIS book is a critical examination of the relationship between old age and sex and conversely the effect of sex on senescence. The author indicates the immense variations in sexual function and responses during old age and urges that the period of old age can be reconditioned, reactivated and made more enjoyable. His thesis is that the retention of sexual vigour throughout the reproductive years is an important way to delay the onset of senescence. This leads to a discussion on modern lines of frigidity and of sterility at any age, and an analysis of the attempts at operative reactivation by Voronoff and Steinach. Scott appears to approve of vasoligature and organotherapy, but warns his readers that such reactivation should be under medical supervision and that self treatment with glandular preparations whether natural or synthetic may well prove dangerous.

The secret of virile old age is the keeping up of a healthy sex interest and an absorbing interest in living. The author draws attention, however, to the fact that any form of sexual excess would cause early degeneration and hasten the arrival of senescence.

The appeal of this book will be mainly to those males who regard senescence "as a tragedy to be avoided at all costs", yet many, perhaps most, senior males are by no means averse to the getting rid of the "tyranny of sex", as Sophocles termed it. Very few women ever have a baby after the age of fifty years, yet two out of three will still be living twenty years later and one will become an octogenarian.

Family interest persists, but personal practice of sex activities and the need for glandular stimulation must surely have a limited field in women who after all form the majority of older people—about four out of every seven aged over seventy-five years in Australia.

**Human Neuroanatomy.** By Oliver S. Strong and Adolph Elwyn; Third Edition; 1953. London: Baillière, Tindall and Cox. 10¼" x 7", pp. 494, with 357 illustrations. Price: 57s. 6d.

THIS third edition appears to be the work of the junior author alone. The book approaches the problem of describing the nervous system in a strictly conventional manner and is almost over-conscientious in the apparent effort of the author to include everything possible. The introductory accounts on cytology, histogenesis and neural development are quite good. The accounts of the peripheral and autonomic systems are, perhaps, overdone, and one wonders what the term "endophylactic-trophotrope" really means. The section on the spinal cord is diffuse and there is practically no mention of lamination in the major tracts. The ascent of the brainstem is laboriously described section by section: treatment is, for the most part, along time-honoured lines, including mention of salivatory nuclei which nobody has ever yet demonstrated, either anatomically or physiologically. The detailed account of the recent work of Magoun and others on the reticular apparatus strikes a new note, but is accorded undue prominence at the expense of more important structures. The cerebellum is treated on reasonably modern lines, but no account of its morphology should ignore the work Elliot Smith did on its subdivisions and the more eccentric of the cortico-ponto-cerebellar connexions. The description of the midbrain is adequate, but some of the assertions concerning dentato-rubro-spinal connexions are open to question and more attention could have been given to localization within the oculomotor nucleus. The account of the diencephalon is a mixed bag. The description of the hypothalamus is conventional, if discursive, but the thalamus is treated badly—almost as much space is devoted to minor intralaminar and mid-line nuclei as to the more important projection nuclei; visual localization is dismissed summarily and the possibility of auditory localization is ignored. In the hemispheres themselves, the basal nuclei and internal capsule are discussed extensively, but the description of the cerebral cortex is sketchy, particularly in the matter of localization. The statement that the "supragranular" layers are lacking in the archipallium is quite out of date, and the account of the rhinencephalon as a whole is a "vintage" piece that takes no account of recent work by Le Gros Clark, Brodal and others. The suggestion that the *corpus callosum* passes through the hippocampus and hippocampal fissure is decidedly original—a perfect compromise between the conflicting views of Elliot Smith and Abbie. Inclusion of sections on blood supply is a good idea, but there are several errors of fact here and it is necessary to be clear over some elementary matters such as whether veins supply tissue or drain it. Throughout, there is discussion of possible function and so far as this might aid comprehension of the text it is valuable. Unfortunately, this aspect is as uneven as the anatomy. Some of the functional accounts are purely snippets taken uncritically from the literature, while in other instances, for example in the case of possible reticular functions, the treatment is over-enthusiastic. It is time, too, that the conception of an "old motor pathway" with its headquarters in the basal nuclei was dropped. This idea was based largely upon work by Rogers on birds and has long since been shown to be incorrect.

The volume is well, indeed lavishly, illustrated and well produced, although there are a number of typographical errors. There is an extensive bibliography, but several authors mentioned in the text do not appear in it. On the whole, we feel that this is not the work from which an uncritical student should receive his first account of the nervous system.

## Books Received.

*[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]*

"Textbook of Obstetrics", by John F. Cunningham, M.D., M.A.O., F.R.C.P.I., F.R.C.O.G.; Second Edition; 1954. London: William Heinemann (Medical Books) Limited. 9" x 6", pp. 600, with 297 illustrations, three in colour. Price: 40s.

The first edition was published in 1950.

"Modern Medicine for Nurses", by Patria Asher, M.D., M.R.C.P., with a Chapter on Mental Ill-Health by Portia Holman, M.D., M.R.C.P., D.P.M.; Third Edition; 1954. London: William Heinemann (Medical Books), Limited. 9" x 5½", pp. 386, with 92 illustrations. Price: 21s.

The book is intended "to help nurses to understand their medical patients and their illnesses".

"Handbook of Tropical Dermatology and Medical Mycology", edited by R. D. G. Ph. Simons; 1953. Amsterdam: Elsevier Publishing Company. London: Cleaver-Hume Press, Limited. Volume II. 9" x 6½", pp. 862, with 510 illustrations. Price: £5 each volume.

Volume I was published in 1952 and was reviewed in these columns in October, 1953.

"The Surgical Clinics of North America"; 1954. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. Chicago Number. 9" x 6", pp. 299, with 75 illustrations. Price: Paper bound, £6 *per annum*; cloth bound, £7 5s. *per annum*.

The number consists of a symposium on gastro-intestinal surgery. There are 22 articles dealing with a wide variety of conditions. It is a "Chicago number".

"The Year Book of Urology (1953-1954 Year Book Series)", edited by William Wallace Scott, M.D., Ph.D.; 1954. Chicago: The Year Book Publishers, Incorporated. 8" x 5½", pp. 376, with 84 illustrations. Price: $6.00.

One of the "Practical Medicine Series" of Year Books.

The Medical Journal of Australia

SATURDAY, MAY 29, 1954.

*All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.*

*References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.*

*Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.*

## RADICAL OPERATIONS OF SURGERY.

ALL medical practitioners will agree with the well-known injunction "*primum non nocere*". They will consent that if no good can be done to the patient by treatment, he should, at any rate, receive no injury at the hands of his medical attendant. When we think of surgical operation, the matter is not so easy to determine as it might appear to be. The newer developments in surgical technique, the introduction of aids such as antibiotics and of drugs such as the sulphonamides, the recent advances in anæsthesia—all these have combined to make it a simple matter for the surgeon, if he wishes to do so, to extend his surgical manipulations so that they may well be described as mutilations. Sometimes the extent of an operation is looked on as a sign of intrepidity and daring on the part of the surgeon in the same way as refusal to adopt such measures is regarded as ultra-conservative. The matter is not easy of determination, and the subject may well repay consideration. Recently, the subject has been discussed in an interesting fashion by two authors. Harvey B. Stone, of Baltimore, has written on "The Limitations of Radical Surgery in the Treatment of Cancer",[1] and I. S. Ravdin, Professor of Surgery in the University of Pennsylvania Medical School, has written on "The Physician, the Patient and Disease".[2] Both these contributions will well repay the study of any practitioner who engages in the practice of surgery; some important conclusions may be drawn from them.

Perhaps it will be well to begin with the concluding part of Stone's contribution. Here he states that in arguments about ultra-radical cancer surgery, the defenders of opposing views sometimes resort to adverse judgements on the qualities of their opponents. He points out that the advocates of the newer radicalism charge those who disapprove of it with lacking in courage and with not having the physical stamina to sustain the long ordeals of radical operations, or the elasticity of mind to welcome innovations. The other group in turn, he states, say that the radicals seek personal prestige and practice at the expense of their patient's interests, that they are handicraftsmen and not physicians, and that showmanship rather than judgement guides them. He points out, and is no doubt quite correct, that there is probably some truth in both sets of charges, but he insists that the great truth is that behind these arguments is the fact that two great conflicting currents are present in every field of human activity. In painting, sculpture, music and literature the advance guard has to face the traditionalist. At every point of history man has been divided into those who wish to improve and correct what they look on as evils, and those who wish to preserve from destruction what they hold to be valuable in the *status quo*. Much of the difficulty attendant on this question will be removed if we remember that the whole development of science depends on the advance of learning and on the building of new structures on the firm foundations which have already been established. In other words, we have to retain what has proved to be good and at the same time engage in reasonable adventure for the search of something even better. Stone puts it well when he remarks that an automobile without brakes is a dangerous agent of destruction and that an automobile without an engine is simply a pile of mechanical junk. Ravdin states that some American surgeons are being carefully scrutinized for operations for cancer which have been called "operations of subtotal evisceration". He adds that other American surgeons practise subtotal evisceration by another means, "by stage operations in which first the appendix is lost, then the gallbladder, and then, if the patient is a female, perhaps a part of the pelvic organs and finally all of them and, subsequent to this, multiple operations for abdominal adhesions". He has recently seen a patient who went through all these operations and in addition had had her spleen removed with three short-circuiting operations of the small bowel, after which she had two intestinal fistulæ. One can quite understand that such a patient from having been "an excellent nursing supervisor" was now a chronic invalid. Stone observes that actual surgery may be employed for either one of two different purposes and that a clear distinction should be made between them. Operation may be employed with the consciously limited objective of palliation of symptoms or for the larger aim of cure. The latter, he thinks, might better be called prolonged and indefinite recovery. Every surgeon of experience can recall cases in which extensive operation has been undertaken with a view to palliation of symptoms and in which this end has been gained. No one will question the usefulness of this type of surgery when it is wisely employed, and one cannot but agree with Stone that there should be no pressure to extend its scope because of "the newer freedom of surgical adventures". He thinks that to make a palliative procedure more radical is a contradiction in terms and ideas. It is in the second type of cancer surgery that a discussion of the "newer radicalism" in the attack on cancer

[1] *Surg., Gynec. & Obst.*, August, 1953.
[2] *M. Clin. North America*, November, 1953.

really centres. In this type of surgery, there is the principle of destroying as much tissue about the growth as can be done with due regard to safety of life and preservation of health and function. Modern surgery does allow this to be done, but Stone adds that the matter is not simple, because one has to determine what is gained by the more extensive surgery and what is lost by it. A gain is to be looked for in an increase in the percentage of long-term survival. Stone thinks that, as yet, an insufficient number of operations have been done over a long enough period to give a clear answer to the question. He refers to a paper by Alexander Brunschwig.[1] In this paper, Brunschwig reported the results obtained by radical resections of advanced intraabdominal cancer in 100 patients. He found that in this series, effective, but in some instances short, palliation was afforded to 35% of patients, with appreciable and prolonged palliation in an additional 15% of the series. Stone points out that the fact that some survivors may live for a number of years is a fact of considerable interest and perhaps of importance. It does not prove, however, that some of the same persons might not have survived also for the same period of time if the usual classical cancer operations had been performed on them, or indeed, if they had not been operated upon at all. In regard to the disadvantages of the newer radical surgery, first thought must be given to the immediate mortality. Stone insists that the immediate mortality should include deaths occurring in the early post-operative period. These are sometimes called hospital deaths to distinguish them from operation room deaths. As an example of radical intraabdominal surgery we shall refer to the photograph of a specimen in Brunschwig's article showing a large carcinoma of the transverse colon, the entire omentum, the spleen, the lower half of the stomach, the transected colon at the hepatic flexure and the transected colon at the junction of the descending portion with the sigmoid. The body and tail of the pancreas and the left adrenal gland were to be seen on the reverse side of the specimen, which is not shown in the illustration. This is certainly heroic surgery, and though it may occasionally be justified, no one would agree that such operations should be countenanced if there were signs of metastases in neighbouring organs or areas. Stone refers to the post-operative experience of survivors of some of these procedures, and he states that in all too many cases, the resulting damage in the form of mutilation, loss of normal functioning, stress and discomfort, and failure to regain weight, strength and normal blood count is unquestionably far greater than after the usual radical operation. These disabilities often continue until the patient's death. Stone puts forward some questions to which he thinks answers should be given. The first is: "What is the probability that we shall shorten the patient's actual time of survival?" The second is: "What is the likelihood that the survival period, long or short, will be one of distress and disability?" The third is: "What is the chance that the patient will be committed to more costly treatment?" Finally, he asks: "What is the chance that the patient will die ultimately of the disease, despite the heroic surgery?" To all these he replies that the probability is great, and in the last instance, very great. At this point, mention should be made of one of Ravdin's arguments that mutilating operations are associated with a profound psychological reaction on the part of the patient and that this is frequently not understood by the surgeon. He states that no attempt is made to tide the patient over the immediate period after operation until such time as a better understanding of the problem makes the patient satisfied with his or her lot.

If we have to sum up this important matter, we would state that if extensive excisions or mutilations are contemplated, the facts should, as far as possible, be made known beforehand to the patient. He should be told what the possible advantages are, and what, as far as is known, will happen if operation is not performed. This has to be done with fairness and with sympathetic understanding. Stone states that explanations to the patient should be made "without either the zeal of salesmanship or the gloom of pessimism". There is no doubt that every case will have to be considered separately and that sight must also not be lost of the fact that by fresh innovations in operative surgery advances may be determined. The whole matter may be resolved by reference to the surgeon's conscience. If he asks himself what he would do in the case of someone near and dear to him, and if he decides then that an extensive operation is desirable after he has looked at the matter from every angle and with honest candour, then his course is clear, he will do his duty and no reproach can possibly be levelled at him. He will also have the satisfaction of knowing that he is acting in accordance with the best traditions of surgery.

[1] *Ann. Surg.*, December, 1945.

## Current Comment.

### MYELOSCLEROSIS.

It is probable that many practising doctors passed their final examination without having heard of myelosclerosis; nor could their examiners take exception to this, for it is a rare disease. It is nevertheless a condition of considerable interest, for it is the cause, in some cases, of the grossest splenomegaly seen in clinical practice, and when the blood dyscrasia becomes manifest (which may be many years after splenomegaly is noticed) the illness runs the course of a refractory or aplastic anæmia. The presence of immature myeloid cells in the peripheral blood, the replacement of marrow by fibrous tissue and the appearance in the spleen, liver, lymph glands, kidneys and other organs of foci containing all elements of blood-forming tissue, so-called myeloid metaplasia, are characteristic features of the disease.

It was first described by G. Heuck in 1879[1] and the subsequent speculation as to its pathogenesis is reflected in the many names that have been devised to describe it: thus agnogenic myeloid metaplasia, aleuchæmic myelosis, osteosclerotic anæmia, *osteopathia condensans disseminata*, among many others. Although Heuck considered that his patient suffered coincidently from two diseases, osteosclerosis and myeloid leuchæmia, and many other diverse opinions as to the ætiology have been held, the orthodox view has been that the marrow is destroyed by some noxious agent, the sclerosis results, and myeloid metaplasia and splenomegaly are compensatory processes by which blood formation is maintained. In management the spleen must be preserved as the major source of the blood elements, inadequate though it is. All this is changing. Final-year students are becoming aware of the disease; it is apparently not so rare, and the compensatory nature of the myeloid metaplasia and splenomegaly is subject to

[1] Heuck, G. (1879), *Virchows Arch. f. path. Anat.*, 78: 475.

doubt. The many names are giving way to the general term myeloproliferative disease, and the pathogenesis, it is suggested, is neoplastic, the fibroblasts as well as the white and red cell precursors developing in parallel in a disorderly and neoplastic manner. In management the spleen may be removed without apparent harm.

W. Dameshek[1] speculated along these lines in 1951 and the concept was suggested by J. M. Vaughan and C. V. Harrison in 1939.[2] The evidence, which is increasing, depends on clinico-pathological surveys, and such a study is that of M. S. R. Hutt *et alii*,[3] in which ten cases are described. The first is a case of pure myeloid leuchæmia with no fibrosis and no anæmia, and the second a case of pure fibrous tissue overgrowth of marrow with reticulum cell hyperplasia and increase in reticulin fibrils. There was no erythropoiesis. The patient presented with pancytopenia and without splenomegaly. The remaining cases show all gradations between these two extremes. One patient had apparent myeloid leuchæmia, but marrow sections showed in addition to the granulocytic hyperplasia a proliferation of reticulum cells with fibrous tissue formation and transition stages between a primitive cell and these two cell types. Another patient suffered from apparent polycythæmia, later developing splenomegaly and immature granulocytes in the peripheral blood. Histology showed excess of immature granulocytes, hyperplasia of reticulum cells, a diffuse network of reticulin fibres, and a striking increase in megakaryocytes in the marrow. Several other cases showed coincidental proliferation of granulocytes, fibroblasts and multinucleate cells which the authors considered on the histological evidence of their sections to be deriving from a single totipotential mesenchyme cell. In the ninth case, that of an elderly man with gross splenomegaly and moderate anæmia, the marrow showed proliferation of reticulum cells and increase in reticulin, no abnormality of granulopoiesis or erythropoiesis, but a striking number of large lymphoid follicles. In their tenth patient, clinically and by marrow biopsy suffering from myelofibrosis, the histology after death showed the typical pleomorphic proliferative picture, but the local arrangement in spleen, lymph gland and liver closely resembled Hodgkin's disease in some cases and reticulum cell sarcoma in others. The authors thus attempt to draw into a single pathogenesis the various types of leuchæmia, polycythæmia, the reticuloses and myelofibrosis suggesting that all these conditions are due to a neoplastic proliferation of a primitive and totipotential cell, the clinical manifestations depending on which particular cell series the process favours.

H. N. Robson[4] reports a similar study describing the features of ten "typical" cases of myelosclerosis and comparing these with seven cases showing mixed and changing pictures. In several polycythæmia and myelosclerosis were coincident. One patient showed typical features of myelosclerosis with hæmoglobin concentration of 7·2 grammes *per centum* and white cells 3700 per cubic millimetre. Sternal trephine biopsy and liver and spleen biopsies showed fibrosis with bone formation and megakaryocytic hyperplasia in the marrow and extramedullary hæmatopoiesis in the liver and spleen. The patient later developed an erythrocyte count of 6,000,000 per cubic millimetre and 16·4 grammes of hæmoglobin per hundred millilitres and a leucocyte count of 90,000 per cubic millimetre; he died of cerebral hæmorrhage.

Perhaps the most convincing evidence against the theory that the splenomegaly is a compensatory process is the fact that splenectomy has been performed in some patients without ill effect. T. W. Green *et alii*[5] report five such cases in which diagnosis of myelofibrosis was made subsequent to operation. In none was there a deterioration in the hæmatological state, and in fact one patient appeared to improve. These authors review 29 other case reports in which splenectomy was carried out. The results did not indicate that harm resulted. Generally speaking, there was no improvement, but the operation may be worth while where the splenomegaly constitutes a disability in itself or where thrombocytopenia or a hæmolytic process appears to be complicating the condition.

[1] *Blood*, April, 1951.
[2] *J. Path. & Bact.*, March, 1939.
[3] *Blood*, April, 1953.
[4] *Australasian Ann. Med.*, November, 1953.
[5] *New England J. Med.*, February, 1953.

## AN ÆTIOLOGY OF SCLERODERMA.

THE introduction of potent remedies into medicine has perhaps tended to lessen the accent on the cause of certain rather obscure conditions. Perhaps for this reason Isidor Mufson, in putting forward the claims of psychological derangement among the possible fundamental causal factors underlying such a disease complex as scleroderma, has been careful to refer to "an" rather than "the" ætiology.[1] Indeed arguments anent the causation of the psychosomatic group of diseases at times appear somewhat shadowy, and lean for proof of their validity upon the results of therapy.

However, we must admit that there is truth in a remark of this author, that an unknown ætiology means a haphazard treatment. The object of his article is to present an analysis of clinical material which points to a somatic background for scleroderma, similar to that believed to exist for Raynaud's disease. In fact, the author goes further and states that scleroderma and Raynaud's disease are one disease, and differ only in the intensity and extent of their pathology. All would not agree with this sweeping statement, but it is at least a starting point. Seven patients were studied and treated. In none of these was any evidence found of an infectious or allergic cause for disease of the small blood vessels. Characteristic features of scleroderma are described in the case histories. Changes in colour of the extremities were common, with the well-known subjective sensations of the Raynaud type, and ulceration was troublesome. Such changes were not confined to the extremities, but were also found in other parts of the body, such as the face. Three patients died from the effects of vasospastic disease associated with organic changes familiar in hypertensive and endarterial vascular disease. The case notes do not suggest any relation between these organic changes and the physiological disturbances which occur in Raynaud's disease and scleroderma, even if we admit the similarity in the two conditions. In discussing the condition, the author states that the primary physiological disturbance in scleroderma is an "increase in the tonus of the precapillary sphincters, which are located at a point where the capillary buds off from the arteriovenous meta-arterioles". Studies have been made of the capillary circulation in the extremities by Mufson, and here he describes a leisurely or intermittent flow. This gives the capillary a beaded appearance, and the arterial limbs are described as narrow and threadlike, while the venous limbs are lengthened, dilated and tortuous. The changes seen in the more severe cases are more persistent, and in severe disturbances the skin remains numb, cold and cyanotic. The author classes the proven organic changes seen in his fatal cases as non-specific.

There is nothing in this which connects the patient's disease with a psychosomatic ætiology; this is supplied by the author in accounts of psychological studies carried out by trained workers. Mufson believes that scleroderma presents a definite psychological pattern, which is in turn due to a characteristic disturbance of the psyche. He sums up his findings by stating that the patient's sense of security always depends upon a commensalistic type of existence. Such persons have a personality of inflexible nature, and destructive changes wrought by circumstance do not permit readjustment, so the author believes. His case histories support this unfavourable type of change,

[1] *Ann. Int. Med.*, December, 1953.

which appears in this series to be associated with exacerbation of the signs and symptoms of the disease. Perhaps we may put the position a trifle more cautiously. The connexion between many forms of skin disease and disturbances of the psyche is generally admitted. Indeed recent literature has appeared in which there is admitted bias in favour of this point of view. It would be strange indeed if a disease like scleroderma, which involves the terminal vascular structures of the skin, remained unaffected by the ups and downs of life, whether small or great. Further, it must be remembered that physical change in the appearance of the integument can and does often, perhaps indeed usually, cause keen distress to sensitive persons, and this inverse factor should not be forgotten. It would be fair to admit that a psychological appraisal of patients who are in the early stages of a disease like scleroderma would be desirable. The knowledge thus obtained might be to devise some control over the functional changes in the skin capillaries while these are reversible. So far as medical literature is concerned, we must remember that evidence must be presented judicially, and small series of cases must be regarded as suggestive only. In the present instance the presence of a dermatologist in the team would have added considerably to the objective accuracy of the descriptions.

## DIET AND CORONARY DISEASE.

IN recent years a spate of articles has appeared on the elusive question of the causation of atherosclerosis, and various findings and conclusions have been related with greater or less justification to the occurrence of coronary artery disease. Perhaps the work that has made the strongest impression on current medical thought is the experimental finding that arterial lesions can be produced in animals by adding cholesterol to their diet; from this it has been inferred that fatty foods are a cause of coronary disease in man, although the inference is really a long way from the actual experimental findings. The relationship of atherosclerosis to diet was reviewed critically in a leading article in this journal earlier this year.[1] A conservative view was taken about much of the work on this subject that has been published, and in particular on some conclusions that have been drawn. Nevertheless, the case against a high fat intake was considered to be so good that it seemed to be wise to recommend that men over forty years of age should not increase their total fat intake, as was commonly done, but should rather decrease it.

The present reference to this well-worn subject is occasioned by certain facts recently brought forward by J. V. Duguid,[2] who thinks that in connecting coronary disease with diet we have oversimplified the problem and taken too much for granted. He points out that the incidence of coronary disease did not seem to decline in England during the war, when the intake of fats was restricted; nor, for that matter, do rabbits with cholesterol lesions tend to die from coronary thrombosis. Duguid, who is professor of pathology in the University of Durham, is concerned primarily with the pathological changes found in arteries on direct examination. He refers to the assumption that atherosclerosis represents a single disease process referable to some particular combination of causes, but goes on to produce evidence to show that lesions which go by the name of atherosclerosis may be the outcome of at least two different processes, with causes which may be quite unrelated to one another. These are mural thrombosis on the one hand and the deposition of lipids or lipid-bearing cells on the other. As Duguid interprets it, the mechanism, in so far as the arteries are concerned, is the same in both processes; solid matter is deposited on the intimal surface and in due course covered with endothelium and incorporated in the intima. This would appear to be a natural reaction of arteries to the presence of solids in their lumen. It is further suggested that in none of the processes are the thickenings the result of changes in the original tissues of the vessel wall, as is visualized in the current conception of atherosclerosis. All are products of substances deposited on the intimal surface; and thus, if this interpretation is correct, we may take it that atherosclerosis is not a specific disease but merely the common end-result of a number of different pathological processes with different causes.

Proceeding on the assumption that in man there are two pathogenetically distinct forms of atherosclerosis, one related to thrombosis and the other of a primarily fatty nature analogous to the cholesterol lesions of rabbits, Duguid states that before arriving at any conclusions about causation we must have some means of distinguishing these forms and of assessing their relative incidence. Unfortunately, most of the lesions found in human arteries are of long standing and have passed through a succession of changes which obscures their origin. However, sometimes certain distinguishing features persist, and one of them is the puzzling phenomenon of narrowing. The presence of narrowing is difficult to reconcile with the view that atherosclerosis represents a degeneration of the vessel walls. A consideration of the normal structure and function of arteries suggests that any change which weakens them or reduces their elasticity should cause them to give way and dilate rather than to become narrowed. The narrowing that is often associated with atherosclerosis cannot be readily explained on any other grounds than thrombosis or embolism. When a thrombus forms in an artery, it occupies the lumen from the outset and so narrows the blood-stream; and although in due course it becomes part of the vessel wall, it does so at the expense of the lumen. There is no weakening of the vessel, but merely a reduction of its effective lumen. With the cholesterol lesions, on the other hand, there is no sudden reduction of the lumen, but merely a gradual silting up of the walls with foam cells. This must have the effect of reducing their elasticity, and it is found that the rabbit's arteries become dilated when they are loaded with cholesterol. It has always been assumed that fatty changes lead to narrowing of the arteries by increasing the intima so that it encroaches on the lumen, but the observed cholesterol lesions show that this is not what happens. Thickening of an artery merely impairs its resilience and leads to dilatation. The only process likely to reduce its lumen is one arising in the lumen itself, such as thrombosis or embolism, and so Duguid concludes that when a coronary artery is narrowed by a fibrous thickening of the intima, thrombosis is the most likely factor involved.

Now, it is a matter of observation that narrowing of the coronary arteries, with all the serious consequences that that implies, is by no means a constant feature of atherosclerosis. In old people, extreme atherosclerosis may be accompanied by little or no narrowing and, conversely, extreme narrowing may occur in arteries which are otherwise not very seriously affected. There are, in fact, according to Duguid, two forms of atherosclerosis—one in which there is narrowing and which is consequently a highly dangerous condition, and another in which the tendency is rather in the opposite direction. Unfortunately, it is not possible to correlate these two forms with lesions regarded respectively as thrombotic and of a primarily fatty nature. For a number of reasons, narrowing is not a constant feature of arterial thrombosis. However, when present, it is a fairly sure sign of that process; and since it is only when there is narrowing that atherosclerosis is likely to be dangerous, it follows that thrombosis is the one factor of importance in fatal coronary disease. Thus the influence of diet on thrombosis constitutes the main part of the problem of the influence of diet on coronary disease.

Duguid suggests two ways in which diet may conceivably play a part in arterial thrombosis. Firstly, it may, by affecting the coagulability of the blood, increase the tendency to clotting. Secondly, by causing fatty changes in the arteries, it may promote mural thrombosis. In relation to the first suggestion, it has been shown that the

[1] M. J. AUSTRALIA, January 9, 1954.
[2] *Lancet*, May 1, 1954.

alimentary lipæmia which follows fatty meals is accompanied by an accelerated clotting time, as determined *in vitro*, but it is not yet known whether an accelerated clotting time *in vitro* actually signifies an increased tendency to thrombosis. It is probably significant that the cholesterol feeding experiments in animals provide no evidence that this is so. The second possibility—that diet may lead to mural thrombosis by damaging the arterial walls—is, of course, the root of the diet hypothesis; but cholesterol feeding experiments undertaken by Duguid and a colleague failed to demonstrate thrombi developing in relation to the cholesterol lesions. Despite extreme disorganization of the vessels, there were never any fibrin formations, and they were forced to conclude that neither an excess of cholesterol nor the consequent arterial lesions were in themselves sufficient to promote thrombosis in rabbits. It is true that in man arterial lesions appear to play a part in the development of mural thrombosis, but there appear to be other essential and probably more important factors concerned. Widespread atherosclerosis of the aorta and other vessels, even with ulceration, has been observed, and yet there has been little or no thrombosis. Speed of blood flow has been suggested as the limiting factor, but this does not provide the whole explanation. It seems likely that there are factors in the blood, possibly anticoagulant substances or fibrinolysins, which in favourable circumstances control fibrin formation and so make arterial lesions potentially less dangerous. On the other hand, there are the converse states which may be described as thrombophilic. Duguid states that in cases of sudden death from coronary thrombosis he has several times noticed that the thrombotic process was not confined to the site of occlusion in the one coronary artery, but was widespread and prominent in the aorta and other vessels. Apparently some thrombogenic influence, more powerful and generalized than mere local damage to the vessel walls, was at work. This, Duguid believes, is the factor that we must aim at controlling if we are to reduce the incidence of coronary disease. It is possible and, indeed, not an unreasonable assumption, that diet may play a part in the production of thrombosis, but the hypotheses so far put forward do not appear to satisfy the facts.

## POOLED PLASMA AND HOMOLOGOUS SERUM JAUNDICE.

THE spread of homologous serum jaundice through pooled plasma has been a matter of great concern, and many suggestions have been made for its control. Most methods of control have been aimed at the elimination of infected donors or the destruction of the virus by such means as ultraviolet irradiation. According to J. G. Allen, D. M. Enerson, E. S. G. Barron and C. Sykes,[1] the answer to the problem lies in storage of pooled plasma in liquid form at room temperature for six months or longer. It is pointed out that the source of virus contamination in the pool of plasma is the occasional unit of plasma derived from a donor who is a carrier of the virus. The carrier-donor cannot be excluded by a history negative for hepatitis or jaundice or by laboratory tests. Therefore, all stores of plasma stored under conditions favourable to virus survival are potentially hazardous. Included in such conditions are the dried, frozen or refrigerated states which are usually employed. On the other hand, the virus of homologous serum jaundice in pooled plasma that has been stored in a liquid state at room temperature for six months becomes attenuated and seldom, if ever, transmits the disease. Allen and his colleagues point out that most viruses do not survive long when stored in a liquid, cell-free medium at room temperature, and virologists carefully avoid exposing viruses to such conditions when they desire to perpetuate virus activity. It has been assumed by some workers that the proteins of liquid plasma stored at room temperature would undergo early and serious deterioration, but this point is denied by Allen and his colleagues. They present data collected over a period of eleven years, comparing their experience with the transfusion of blood only, of plasma only, and of blood and plasma. The figures presented support their contention that there is little if any risk of homologous serum jaundice associated with the administration of pooled plasma after it has been stored at room temperature for six months prior to administration, provided the donors are healthy and meet the standards set up by the National Institutes of Health in relation to a history of hepatitis and jaundice. If, however, the donor requirements of the National Institutes of Health are set aside, and pools of plasma are deliberately contaminated with plasma drawn from patients suffering from homologous serum jaundice at the time of giving their donation, a period longer than six months is necessary to render this highly virulent product free of risk of homologous serum jaundice. Chemical studies of liquid pooled plasma show no clinically significant alteration after room-temperature storage for thirty months, and it is stated that clinical studies reveal this plasma to be as useful in the prevention or treatment of shock or hypoproteinæmia as freshly prepared liquid or dried plasma. Thus, if we are to accept the experiences of Allen and his colleagues, the storage of pooled liquid plasma for six months or longer becomes an inexpensive and practical means of inactivating the virus of homologous serum jaundice. Thereafter, this plasma can be lyophilized (dried) without difficulty if it is desired to store it indefinitely. It is pointed out that the clotting factors are lost too rapidly at room temperature storage for the plasma so stored to be useful in the treatment of disorders of coagulation, but this is not objectionable, since fresh plasma is of little benefit in the treatment of abnormal bleeding disorders other than hæmophilia. It is suggested that the treatment of coagulation disorders which respond to plasma components is best given by the administration of appropriate plasma fractions rather than of the intact product. As might be expected, storage for six months at room temperature in the manner described, while satisfactory for plasma, is not adaptable to whole blood.

[1] *J.A.M.A.*, January 9, 1954.

## ACUTE OSTEOMYELITIS.

THE introduction of penicillin made possible a more conservative approach to the treatment of acute osteomyelitis and greatly improved the final outcome, especially in relation to mortality. Just how far the conservative attitude may be taken is debatable. The old extensive drainage operations are happily no longer needed, but general opinion has not supported those at the other extreme who have advocated no local interference except when pus forms outside the bone. In general the decision is between open operation, including drilling of the bone, and a more conservative measure, such as the aspiration of pus. These methods were used alternately by A. E. Bremner, G. A. Neligan and C. K. Warwick[1] in a series of 23 selected patients in the period 1949-1951. The series is relatively small, but the investigation was carried out carefully and the period of subsequent observation is satisfactory; so the results are of value. The main criterion adopted for assessing the results was the duration of disability after treatment was started. By this criterion there appears to be no significant difference between the results with the two methods, and no important difference was found in respect of any other criteria. In the light of this, Bremner, Neligan and Warwick, for obvious reasons, selected the conservative method for their own practice, and they state that the results have been satisfactory so far. However, they are of the opinion that success with this method demands a high standard of clinical judgement, with daily reassessment, and may not be achieved constantly except in centres where many cases of osteomyelitis are met with. Perhaps, when these requirements are lacking, it is safer to adopt the less conservative method, which has its own strong advocates in any case.

[1] *Lancet*, May 8, 1954.

# Abstracts from Medical Literature.

## ORTHOPÆDIC SURGERY.

### Tuberculosis of Bones and Joints.

M. C. WILKINSON (*J. Bone & Joint Surg.*, May, 1953) states that the main object of operations on tuberculous bones or joints is to heal the local lesion. He describes how far such operations, when combined with constitutional treatment and antibiotic therapy, have been successful in preserving joint function and reducing the time required for treatment. He states that there is usually a concomitant infection of synovial membrane and the ends of the long bone. Local endarteritis is one of the main features of the pathology of tuberculosis. In consequence, ischæmic necrosis is a common and early feature of the pathology of skeletal tuberculosis. Once this has occurred, antibiotic drugs can reach the affected part only with difficulty unless the way is opened by curettage of necrotic foci. Not only may ischæmic necrosis occur in bone, but the synovial tissues and capsule become engorged and congested. The author states that the results of partial synovectomy, partial capsulectomy and curettage of necrotic foci in bone appear to be satisfactory. After such operations the tuberculous process appears to be arrested and recalcification occurs; partial synovectomy and capsulectomy alone seem to be beneficial in those cases in which no major necrotic areas are seen. Twenty-three patients have been discharged from hospital after operation for spinal tuberculosis by means of evacuation of the abscess and curettage of granulomatous material. Two chief groups of patients were selected for operation: those whose disease had recurred after previous constitutional treatment, or for whom operation was performed to accelerate and improve the results of initial treatment; and those with unstable ankylosis and developing deformity, in whom curettage of the lesion was followed by the insertion of bone chips into the resulting defect. Twenty-three children and four adults with tuberculosis of the hip have been treated by partial synovectomy with or without curettage of necrotic foci. In the adults the cartilage of the femoral head was found to have been destroyed by the disease, possibly because operation was performed too late. Of the 23 children, treatment was successful in 19, in that the disease rapidly became quiescent after operation and a good range of movement was restored; in two cases it was partly successful; in two it failed. The average duration of treatment in the favourable cases was ten months. Splints have not been worn by patients discharged. No patient discharged has suffered a relapse. The author points out that in tuberculosis of the knee destruction of cartilage usually occurs late; even before the introduction of antibiotics, recovery with useful movement was sometimes possible in childhood. In adult life, recovery with a useful range of movement was rare. Sixteen patients, seven of whom were children and nine of whom were adolescents or adults, have been treated by means of a combination of antibiotic treatment and synovectomy. The results in these cases are encouraging. The author concludes that in patients with tuberculosis of the spine, especially in the thoracic region and when perispinal abscess-formation is a prominent feature, the treatment helps to ensure stable ankylosis in the type of case in which it otherwise might not occur. In children with tuberculosis of the hip, and in adults and children with tuberculosis of the knee, it is usually possible to save the joint and to restore function, provided the joint has not been destroyed before treatment is begun.

F. HARWOOD STEVENSON (*J. Bone & Joint Surg.*, February, 1954) states that the bactericidal antibiotics penicillin, streptomycin, iso-nicotinic acid hydrazide (isoniazid), bacitracin and neomycin, and the bacteriostatic antibiotics aureomycin, chloramphenicol, terramycin and PAS, and the sulphonamides, if used together, may be ineffective. The bactericidal antibiotic which acts upon actively dividing organisms may be prevented from so doing by the bacteriostatic antibiotic inhibiting cell division. Thus aureomycin or chloramphenicol may diminish the effect of penicillin; terramycin has been shown to diminish the effect of isoniazid against tuberculosis. Streptomycin, on the other hand, may help penicillin to cure staphylococcal infection by preventing the emergence of penicillin-resistant staphylococci. It may therefore be necessary, if streptomycin and isoniazid are being used, and another antibiotic is proposed for use against a secondary invader, to test in the laboratory the effect of a combination of the drugs upon the secondary infecting organism. No antibiotic for tuberculosis should ever be given alone. Streptomycin in doses of one gramme daily and isoniazid in doses of four milligrammes per kilogram of body weight daily form the best chemotherapeutic combination at present available. Since many patients will require chemotherapy for more than three months, and the above-mentioned combination cannot be guaranteed to prevent resistance from developing beyond that time, it is at present better always to use PAS in a dosage of at least 15 grammes per day with the other two drugs. The antibiotic treatment of secondary infection may require detailed laboratory investigations if antagonism between drugs is to be avoided. Patients admitted with reactivation of the disease frequently give a history of injury. An instruction to patients after discharge from hospital to report any reasonably serious injury, so that they may receive a timely course of chemotherapy, may prevent or diminish such relapses. The author states that it should be possible to promote healing by chemotherapy in over 90% of cases of persistent sinus if surgery is employed in a proportion of them—namely, those which demand surgery on radiological grounds and those which do not show evidence of healing within two months of intramuscular streptomycin therapy. The average duration of conservative treatment, before the beginning of reossification, was reduced from fifteen months to seven months, and approximately 40% of patients with intraarticular hip disease regained a range of movement not seen in the pre-streptomycin series. In both series good results were obtained in cases of extraarticular hip disease, and the difference was therefore probably less significant. With synovial tuberculosis of the knee the results were much better from streptomycin treatment than those ordinarily expected in a similar consecutive series without streptomycin. In the opinion of many recent writers, chemotherapy has its greatest value in restoring to tnuberculosis-inoculated tissues their powers of healing and thereby allowing tuberculous bone and joint disease to be tackled upon the ordinary principles of surgery. The author concludes that streptomycin and the newer antibiotics have already belied the pessimistic agnosticism of 1947. In certain instances, notably in disease of the knee and hip, and in some cases of draining sinuses, it appears that they are sufficient to produce a quiescence which may be a cure.

### Intrinsic Contracture in the Hand and its Surgical Treatment.

CRAMPTON HARRIS AND DANIEL C. RIORDAN (*J. Bone & Joint Surg.*, January, 1954) state that intrinsic contracture in the hand is a crippling entity which is often unrecognized. The hand assumes a typical position with flexion of the metacarpo-phalangeal joints and extension of the interphalangeal joints. The thumb may be involved and may exhibit marked flexion of the metacarpo-phalangeal joint and hyperextension of the interphalangeal joint. The loss of function is considerable—the patient loses the essential functions of pinch and grasp. There are many possible causes—ischæmia of the small hand muscles, spasm of the intrinsic muscles as found in rheumatoid arthritis and leprosy, and fibrosis resulting from direct trauma or thermal injuries. The treatment of choice is active splinting coupled with selective surgical excisions of the extensor aponeurosis, as suggested by Littler. The oblique fibres of the extensor hood are removed, and this releases the extensor contracture; but the transverse fibres are preserved, thus retaining interphalangeal extension. This is best done through a single dorsal mid-line incision. Post-operatively, the patient's hand is splinted with the metacarpo-phalangeal joints at 180°, but with the interphalangeal joints left free for the active motion that is to begin on the first post-operative day. By means of active splinting and this relatively simple surgical procedure the vital functions of pinch and grasp are restored to the intrinsically contracted hand. The authors state that they have performed this operation on twelve patients. Good results were obtained in all of them. One of the early patients in the series demonstrated slight clawing of one finger, due to excessive resection of the transverse fibres of the extensor aponeurosis. This difficulty was not encountered in the later cases in the series.

### Idiopathic Scoliosis.

J. I. P. JAMES (*J. Bone & Joint Surg.*, February, 1954) states that idiopathic scoliosis can be classified according to patient age groups, infantile, juvenile and adolescent. There is no evidence that any form of conservative treatment influences the prognosis; indeed, most of the patients with mild curves received no treatment, whereas those with severe curves have all received vigorous and varied conservative therapy over many years. Idiopathic scoliosis is a three-curve or four-curve arrangement. In the former case the middle curve of the three is primary, in the latter the middle curve of four.

The primary curves retain rotation on forward flexion, whereas the compensatory curves do not, except to a minor degree in some long-standing cases. Clinical examination is better than radiography to determine which is the primary curve, and rotation is the significant sign in establishing the curve pattern. Occasional intermediate patterns with minimal rotation in the lumbar region offer difficulty in diagnosis between the three-curve and four-curve patterns. The lumbar and perhaps the combined thoracic and lumbar scolioses never need correction, although fusion may be indicated for pain. Thoraco-lumbar curves rarely require correction and fusion, and so good is the general prognosis that it is better to await the development of deformity, although a prominent hip may be most conspicuous even when the curve is small. In thoracic scoliosis the situation is different. When the onset is in adolescence, perhaps half of all patients may be expected to develop a severe curve; with a curve of juvenile onset the proportion is over 80%, and with an infantile it is over 90%. Severe scoliosis is not in itself an invariable indication for radical treatment, but a curve with a bad prognosis in degree of curvature and appearance obviously demands surgery. If the curve pattern and age of onset are considered together, accurate prognosis is possible. Correction and fusion may then be confidently advised for the prevention of future deformity. Correction of well-established curves is difficult, and the rib rotation remains. In young patients, before deformity is serious, correction is relatively easy and more complete, but the author has hesitated so far to operate before the age of ten years. If spinal fusion in adolescence proves satisfactory, it may be possible to intervene at an earlier age.

## PÆDIATRICS.

### Bilateral Encapsulated Subdural Effusion Complicating Meningitis.

J. A. EPSTEIN AND S. E. GOLDZIER (*Arch. Neurol. & Psychiat.*, February, 1953) report a case of *Neisseria meningitidis* meningitis in an infant, aged ten months, who, after adequate treatment with antibiotics, developed a bilateral encapsulated subdural effusion necessitating surgical (and successful) removal. The authors state that this complication had appeared only since the advent of therapy with sulphonamides, penicillin and the newer antibiotics. They found reports of 39 cases in the literature, occurring in the course of bacterial meningitis caused by a variety of organisms. The pathogenesis of the lesion and the clinical features leading to early diagnosis are discussed, together with the management of the case.

### Treatment of Hypertensive Phase of Acute Nephritis.

S. W. ROYCE (*Pediatrics*, October, 1953) used "Veriloid", a derivative of *veratrum viride*, in the treatment of the hypertensive phase of acute nephritis in six children. In each child hypertension was relieved and an encouraging clinical response obtained. The intravenous route of administration was employed, and a constant check on the children's blood pressure was considered necessary. The author states that the deaths which occur early in cases of acute nephritis are at least partially due to a rapid rise in blood pressure. Many hypotensive agents have been tried, but all have disadvantages. Magnesium sulphate, the one most commonly used, is unpredictable in its effect and has a narrow margin of safety. "Veriloid" produces hypotension through the central nervous system, not through a peripheral action on the autonomic system. It causes vagal stimulation of the heart and increased renal blood flow. Whether it is really necessary to lower the blood pressure in any particular case requires careful consideration before using a hypotensive agent.

### Short-term Administration of Corticotrophin for Active Rheumatic Carditis.

M. G. WILSON, H. N. HELPER, R. LUBSCHEZ, K. HAIN AND N. EPSTEIN (*Am. J. Dis. Child.*, August, 1953) administered 32 courses of corticotrophin to 28 patients with active rheumatic carditis. In 24 patient-courses arrest and reversal of signs of carditis were produced within a few days by this form of treatment. Apart from transient minor recurrence on cessation of therapy in two, the cardiac status was maintained in the majority for more than six months. Of eight patients who had inadequate therapy, as judged by a rise in the number of eosinophile leucocytes to more than 10 per cubic millimetre during therapy, five had a recurrence of carditis. It was concluded that the course of the disease with corticotrophin therapy differed greatly from the natural course, and that it was of great importance that this treatment should be given early in the course of the disease.

### Diarrhœa of Allergic Origin.

P. E. ROTHMAN (*Am. J. Dis. Child.*, August, 1953) presents a review of allergic diarrhœa in infancy. Two main groups are considered: (i) severe diarrhœa during the neonatal period with rapid loss of fluid and electrolytes and impending death, (ii) chronic diarrhœa during the second year of life simulating cœliac disease. Mild cases occur with great frequency in both groups. Clinical diagnosis is often difficult, and little help is to be expected from laboratory examinations or skin testing. On reasonable diagnostic suspicion in the first group a soy bean milk, a meat formula milk or "Nutramigen" may be tried. Patients in the second group have been described as suffering from "mucous disease", "chronic intestinal indigestion" and "steatorrhœa associated with intestinal allergy", or as "mild or near cœliacs". A trial diet is suggested, such as one consisting of lean meat, potato, rice, apple, banana, pear and weak tea (any sweetening being done with saccharin); other foods are added singly at intervals if the clinical response is satisfactory. Drugs are not of value.

### Infantile Renal Acidosis.

R. LIGHTWOOD, W. W. PAYNE AND J. A. BLACK (*Pediatrics*, December, 1953) present evidence that infantile renal acidosis is a clinical entity with characteristic symptoms and biochemical findings. The data on 35 cases are discussed. The authors state that clinically there is failure to thrive, with constipation, vomiting, anorexia, irritability, or apathy, hypotonia and dehydration starting from the fourth and continuing to the sixth month of life. Biochemically there is hyperchloræmic acidosis with neutral or alkaline urine. Radiological evidence of renal calcification was present in 13 cases. A few leucocytes are often found in the urine, though it is sterile. The differential diagnosis is large, including pyelitis, pink disease, Fanconi rickets, idiopathic hypercalcæmia, vitamin *D* intoxication, and *diabetes insipidus*. Eight mildly affected infants were allowed to recover without treatment, the remainder being treated with alkalis (as citrate, lactate or bicarbonate) under biochemical control. All the infants recovered. The condition is thought to result from an imbalance in the normal post-natal development of renal tubular function.

### Induced Renal Hyperchloræmic Acidosis.

S. ISRAELS, G. E. DELORY AND B. GOURLEY (*Pediatrics*, January, 1954) gave a carbonic anhydrase inhibitor (*Number 6063*) to a mentally defective infant, aged eight months, who showed no evidence of renal dysfunction. After administration of the drug the serum alkali reserve and serum sodium content fell, the serum chloride level rose, and the urine became less acid. The "total carbon dioxide" excreted in the urine also increased. There were no symptoms associated with these biochemical changes. The results indicated that the biochemical changes produced by administration of this carbonic anhydrase inhibitor were indistinguishable from those found in infantile renal hyperchloræmic acidosis and raised the question whether diminution of carbonic anhydrase activity might be the causative factor in this disease.

### Diabetes Insipidus in Infancy Resistant to Pitressin.

M. Y. KAO AND M. M. STEINER (*Pediatrics*, October, 1953) report the case of a male infant who suffered from persistent vomiting, failure to gain weight, polyuria, erratic fever and periods of dehydration, associated with an inability to secrete urine of high specific gravity and high values for serum sodium and chloride content. There was no antidiuretic response to the injection of pitressin or to intravenous infusion of hypertonic saline. Such a condition has been described before as a familial one, occurring only in boys, except for one reported exception. It is considered to be the result of a failure of end-organ response in the kidney.

### Composition of Sweat in Cystic Fibrosis of the Pancreas.

P. A. DI SANT'AGNESE, R. C. DARLING, G. A. PERERA AND E. SHEA (*Pediatrics, November, 1953*) have drawn attention to the adverse response to heat of patients with cystic fibrosis of the pancreas. They state that reported cases have shown free sweating, and an abnormally low serum chloride content has been demonstrated twice. They have found that the sodium and chloride concentrations of sweat from 43 patients with fibrocystic disease of the pancreas were two to four times higher than normal. There was a lesser rise of sweat potassium concentration. They consider that massive salt loss through sweating in hot weather accounts satisfactorily for the "heat casualties" among those suffering from cystic fibrosis of the pancreas.

# Special Articles for the Clinician.

(CONTRIBUTED BY REQUEST.)

## C.

## ASPHYXIA NEONATORUM.

Shall man into the mystery of breath
From his quick beating pulse a pathway spy?

—GEORGE MEREDITH.

LIFE'S first and shortest journey may occasionally be its most dangerous, for, apart from other hazards, it may end in an unsatisfactory establishment of respiration. At the end of this journey the fœtus is called upon to take its most difficult breath.

Respiration at birth may be established in one of two ways.

Firstly, it may arise from nervous stimuli acting on a perfectly normal and uninhibited fœtus as its head is born, so that breathing and crying may occur at this stage of incomplete birth. The nervous impulses may not have their effect until immediately after complete delivery, but in either case the respiratory centre is receptive and is prepared to commence rhythmicity following the reception of simple peripheral stimulation. This type of breathing is usually regular, and the baby causes delight to all.

Secondly, the initiation of respiration may have to await chemical stimuli if the nervous stimuli fail. These chemical stimuli are most probably a combination of carbon dioxide excess and oxygen lack acting on the carotid body and aortic arch and from here through the reflex drive to the respiratory centre. The period of apnœa, whilst this chemical stimulus is being awaited, may vary from half a minute after birth to even three or five minutes or longer. During this period the baby's pulse rate gradually becomes slower. The less receptive the respiratory centre, whether owing to immaturity, trauma, drugs or anæsthesia, the longer will this period of apnœa last, until in the extreme case breathing will never commence. Often this period of apnœa is ended with a gasp rather than regular respiration. It seems that the gasp is just sufficient to get enough oxygen through the alveoli and thus to the respiratory centre. Barcroft describes this most aptly by saying: "The dying fœtus in its last effort . . . opens the door to life and a free existence."

With this simple yet fundamental understanding of the method of initiation of respiration we may now consider prevention, types and management of *asphyxia neonatorum*.

### Prevention.

Prevention of the condition is one of the most important aspects, and without considering all the causes of intra-uterine asphyxia, let me mention the man-made ones which occur too often and should be avoided.

Excessive use of, and bad timing of, drugs which may depress the respiratory centre of the newborn should be carefully controlled. Particular care should be exercised when handling premature labours. Morphine given within a short time of birth often, but not always, causes some respiratory depression in the baby.

Morphine has a limited place in normal labour. Pethidine *per se* appears to have little effect on the newborn's respiration, yet if it is combined with other drugs, such as hyoscine, the effect may be more positive. Particularly is this so if barbiturates have been used previously. The amount and combinations seem more important than any one particular drug, so that cases in which drug asphyxia may be noted are those of long or "difficult to manage" labours, and labours in the toxæmic or in the uncooperative patient who forces the use of more sedation than is good for the baby. These cases are in complete contrast to those of the cooperative and "educated for childbirth" patient, who so often has a shorter labour almost free of drugs and anæsthesia. In these cases the babies need no resuscitation.

The type and duration of anæsthesia have a positive effect on the production of asphyxia, and probably more important is the ability of the administrator. Anæsthesia is often the main cause of *asphyxia neonatorum*, so that even the shortest anæsthetic should be well given, and is one aspect of obstetric training which requires more stress. There is little doubt that nitrous oxide and oxygen anæsthesia well given is one of the best all-purpose obstetric anæsthetics available for vaginal deliveries. Local infiltration is free of ill effects on the baby but has its own disadvantages.

### Types.

If our prevention methods have been carefully thought of and practised, then what conditions in the newborn are we likely to encounter that will produce an asphyxiated baby? These may be summarized as follows: (*a*) Those in which asphyxia is consequent upon the shock of a difficult delivery, for example, a breech extraction or a difficult forceps delivery (particularly with ether anæsthesia). (*b*) Those in which the infants have their own inherent cause for the asphyxia: (i) impaired airway—mucus, stricture; (ii) impaired lungs—atelectasis (more often after Cæsarean section), hyaline membrane formation, hiatus hernia, pneumonia; (iii) defective heart action—congenital defect (this type of cyanosis is often not considered under the heading of *asphyxia neonatorum*); (iv) defective respiratory centre—due either to trauma during delivery or to immaturity. There would appear to be no fixed point in the development of the respiratory centre above which it is capable of functioning and below which it is not. Some premature babies weighing one and a half pounds appear to have a respiratory centre capable of functioning, and others of two pounds or more have not. It is most likely that there are other factors concerning the development as a whole of each baby as well as that of the respiratory centre or centres.

### Management.

What then should we do for the baby that does not breathe immediately or shortly after its birth?

Firstly, aspirate the upper air passages. Actually this should be done in all births as a routine, but in the baby not breathing it is wise to repeat the aspiration to convince yourself firmly that there is no loose obstruction present. There are many aspirators available, and provided they are used carefully no harm to delicate structures should result. This method of aspiration can clear the passages only as far as the vocal cords. To go further one needs special instrumentation, and these bronchoscopic methods are rarely used; the simple oro-pharynx aspiration together with a slightly head-low position for postural drainage gives excellent results. Obviously the earlier aspiration is carried out, the less chance the baby has of taking any fluids down its bronchi.

Secondly, handle the baby carefully, and if after sixty to ninety seconds there is no sign of the first breath, then it is advisable, in most cases of this type, to separate the baby, keep it warm and lay it slightly on one side or the other with the head lowered.

Thirdly, have oxygen available in the naso-pharynx in readiness for the first breath. It may be delivered to the baby by a fine intranasal catheter, or better still the baby will benefit more by being placed in an incubator with an oxygen flow of about four litres per minute. The incubator will admirably serve the second and third requisites—that is, provision of warmth and oxygen. It is the generally accepted practice to use a temperature of from 91° to 93° F. in the incubator. It is of interest to note, however, that experiments have been carried out in the United States of America employing chilling methods to lower the metabolic rate and thus reduce the oxygen requirements. The writer has had no experience of these methods.

The baby having been cared for as outlined under these three headings will usually be found to have a pink colour and this, even in the absence of any visible respiratory movements. Skin absorption of oxygen is possible, although, to my knowledge, no agreed-upon scientific percentage absorption has been determined. Another real benefit of the incubator is that no clothing is required, and therefore it cannot hamper any respiratory or other movements of the baby. Observation of the whole of the baby is unrestricted, and the "hands off" policy is easier to maintain.

High oxygen concentrations, used to save the lives of atelectatic premature babies, are receiving the blame for the development of retrolental fibroplasia today, and some definite scientific proof of this in kittens has recently been published (Ashton). One does not advocate a higher oxygen percentage than that required to keep the baby a good colour, and intermittent rather than continuous use should be practised. It would appear that an oxygen atmosphere in excess of 60%, particularly when one is dealing with a premature baby weighing under three pounds, is to be avoided.

Your own restlessness, if present during this testing time for all, should be seriously controlled; but if it becomes overwhelming and you feel you must do something, then do no harm. Think of α-lobeline and inject 3 milligrammes ($^1/_{20}$ grain) into one buttock (baby's). This drug acts through the carotid body (same site of action as the chemical stimulus that we are awaiting); so that it seems reasonable to use it in order to give the respiratory centre a "kick", in the same sense as this term is used with regard to starting an engine. It is all that we can expect from lobeline apart, of course, from the peripheral stimulation of the needle prick.

The above measures will be effective, almost invariably, in the baby who is undamaged, and breathing will have commenced. This baby has just been slow to breathe, probably owing to a drug effect or anæsthesia. On the other hand, the baby that does not breathe after this management has a grave prognosis, for it is usually found that those who pass this period of three to five minutes without recovering have some firm reason for doing so. They have some serious congenital defect or have been damaged during labour to such an extent that some link in the essential chain is absent.

What other methods of initiating respiration may be attempted? Some form of peripheral stimulation may be attempted, such as gentle movement of the baby, but one should resist any more drastic measures, such as hot and cold contrast baths. Mouth-to-mouth insufflation has its advocates, as also has Eve's rocking method. Artificial respirators of the Drinker type are used in some schools with some success. Artificial respiration by chest compression and relaxation can hardly be expected to have any effect on lungs which are as yet unexpanded. These methods are used with a pious hope and are so often associated with failure that they cannot be recommended.

Intragastric administration of oxygen is simple and may be a useful means of introducing oxygen whilst one is waiting for pulmonary respiration to commence. There is quite a good description given by Akerrén and Fürstenberg. A limited experience of this method has not encouraged the writer to abandon the incubator in its favour.

What of the baby that lives but does not establish one of the normal rhythms of respiration?

It may be suffering from some form of cerebral damage, atelectasis or a developmental defect such as hiatus hernia, or perhaps more simply a "failure of conditioning for pulmonary respiration".

The differential diagnosis is usually difficult. The respiratory rhythm of the "cerebral" baby is often erratic and associated with some body or limb twitchings. If it attempts to cry when handled, it does so with a weak and miserable response. Moro's reflex may be elicited, and on lumbar puncture blood-stained or xanthochromic fluid will usually confirm the diagnosis. One can only wait on this baby with careful management and vitamin *K*.

The atelectatic baby usually has a marked indrawing of the lower part of the sternum and ribs; twitchings may also be present, but other signs of cerebral irritation are not. When the oxygen concentration is increased, the colour improves; but the condition persists and will kill if of a severe degree. Auscultation and X-ray examination of the chest often do not help in diagnosis. The alveoli at birth are usually unexpanded and appear to have "sticky" walls, and all newborns suffer some degree of atelectasis, even the apparently healthy and crying babies, for it requires some days for complete expansion to occur. The more severe the degree of atelectasis, the more urgent the need for help. Professor Virginia Apgar, of New York, last year was experimenting with sudden short positive pressure impulses in order to open the alveoli, but so far it has been found that positive pressure methods *per se* are unsatisfactory; when combined with a thoracotomy and exposure of one lung they may be more effective.

The case of hiatus hernia is not so rare as was previously thought, and with routine autopsies more are seen. It may produce much the same clinical picture as atelectasis, which in fact it causes, by reason of the abdominal contents being in the thorax. The only way of saving the life of this child, because of its progressive distress, is to open the chest and replace the abdominal contents and close the hernial orifice.

Admittedly these last few thoughts are in a specialized field, but nevertheless more will be heard of these methods, so it seems reasonable to mention them.

Failure of "conditioning for pulmonary respiration" is sometimes met with in the full-time baby born very easily by elective lower segment Cæsarean section. It often cries when delivered and then shortly afterwards begins to develop cyanosis and fails to establish a regular respiratory rhythm. Treatment of these babies has sometimes been most disappointing, and at autopsy no cause other than atelectasis has been found to account for death. These cases provide most convincing evidence that lifting the baby out abdominally, however easy, is not as good for it as a safe and well managed vaginal delivery.

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## British Medical Association News.

### SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on December 3, 1953, at The Saint George Hospital, Kogarah. The meeting took the form of a number of clinical demonstrations by members of the honorary medical and surgical staffs of the hospital. Part of the report of this meeting appeared in the issue of May 22, 1954.

#### Surgery in Peptic Ulcer.

DR. R. P. MELVILLE showed four patients to illustrate the results of surgery in peptic ulcer. The first was a man, aged fifty-five years, who had suffered from pain in the epigastrium for nine or ten months; it was more severe after eating. He could take only a small amount of food, suffered from a feeling of fullness and discomfort and from loss of appetite, and had lost one stone in weight in twelve months. At times he had eructations of foul-smelling gas. Physical examination of the patient revealed no abnormality. X-ray examination after a barium meal revealed some pyloric deformity, but no ulcer. A blood count was within normal limits. At laparotomy on April 2, 1952, a small indurated ulcer was found on the posterior surface of the lesser curve, two inches from the pylorus. Partial gastrectomy was performed, with high ligation of the left gastric artery and vein. After the operation retention of urine was troublesome. The patient was discharged from hospital on April 20. Pathological examination of the specimen removed showed it to be a simple peptic ulcer. Dr. Melville said that during the early post-operative period the patient had had occasional eructations of bile and flatulence, but at the time of the meeting he was able to eat normal meals with no dietetic restrictions. Before operation his weight was 9 stone 13 pounds; at the time of the meeting it was 11 stone 10 pounds; his normal weight was 12 stone. The period of recovery from operation to full working capacity was three months.

Dr. Melville's second patient was a man, aged thirty-eight years, who had a long history of duodenal ulcer, with two perforations at intervals of three months. He underwent subtotal gastrectomy and his convalescence was uneventful. At the time of the meeting his condition was as follows. He had to reduce the size of his meals because of discomfort if he ate too much, and he had to rest from physical effort. He avoided bulky foods, puddings *et cetera*. His weight was 11 stone 9 pounds, his pre-operative weight was 11 stone 6 pounds, and his normal weight was 11 stone 12 pounds. The period of recovery from operation to full working capacity was nine months.

The third patient shown by Dr. Melville was a man, who had had a perforated duodenal ulcer in 1945 and had never been really well since; he had suffered from recurrent hæmorrhage and pain. He had been confined to bed on 12 or 13 occasions with minor hæmorrhages, and had had a severe hæmatemesis in November, 1950, and again prior to his admission to hospital. Four litres of blood were given by transfusion prior to operation. Subtotal gastrectomy was performed on August 20, 1951, and he was discharged from hospital on September 2 after an uneventful convalescence. Up to the time of the meeting he had had no pain or further hæmorrhage; he was able to eat a normal meal and had no

postprandial discomfort. His weight was nine stone three pounds; prior to operation it was under nine stone, and his normal weight was ten stone two pounds. The period of post-operative incapacity was nine months.

Dr. Melville finally showed a married woman, aged fifty-eight years, who had a long history of gastric ulcer with perforation, treated by oversewing. The symptoms persisted, with deformity of the stomach. Partial gastrectomy was then performed; two large gastric ulcers were found on the lesser curve, and a duodenal ulcer was also found. At the time of the meeting she had no postprandial symptoms. Her weight was nine stone two pounds; prior to operation it had been about seven stone, and her normal weight was nine stone six pounds. She had achieved full working capacity in two months after operation.

### Adenocarcinoma of the Ampulla of Vater.

DR. W. J. PULLEN showed a married woman, aged sixty-four years, who had undergone local resection of an adenocarcinoma of the ampulla of Vater. She had been well till a few months prior to her admission to hospital, when she began to notice that her appetite was poor and that she was belching a lot. About one month before her admission she experienced a severe attack of pain in the right hypochondrium radiating to the back and associated with vomiting. She became jaundiced. This attack settled down fairly quickly and the jaundice disappeared. A cholecystogram suggested a non-functioning gall-bladder, and accordingly she was admitted to hospital for cholecystectomy. There had been no previous serious illnesses, but she had lost half a stone in weight in the previous two months.

On examination, the patient was a slightly built woman with a suggestion of yellow sclerotics. However, there was no bile in the urine. Tenderness was present in the right hypochondrium, but no tumours were palpable. Her blood pressure was 160 millimetres of mercury, systolic, and 100 millimetres, diastolic. Operation was postponed for a week because of an attack of "cholecystitis" with vomiting. Through a right upper paramedian incision the gall-bladder was found to be distended, but was not inflamed, and it contained no stones. The common bile duct was opened and it was found impossible to pass dilators through into the duodenum. Accordingly, the duodenum was opened and a hard plaque, measuring one and a half inches by half an inch by half an inch, was found surrounding the ampulla of Vater. This was locally resected with a wedge of healthy tissue. The common bile duct and pancreatic ducts were anastomosed into the second part of the duodenum over rubber and polythene tubes respectively. The duodenum and common bile duct were closed, and the abdomen was closed with a tube down to the operative site. The post-operative course was entirely uneventful and the patient was discharged from hospital two weeks later. The pathological report by Dr. A. E. Gatenby was as follows: "The tumour is one inch in diameter with a central hole and section of two ducts. It shows the structure of a diffuse infiltrating adenocarcinoma of the duodenal mucosa. It apparently arises at the ampulla of Vater." Dr. Pullen said that at the time of the meeting, two months after operation, the patient felt better than she had felt for many months and had gained half a stone in weight.

### Perforated Adenocarcinoma of the Jejunum.

Dr. Pullen's second patient was a man, aged sixty-two years, who had had a perforated adenocarcinoma of the upper part of the jejunum. He had experienced pain in the upper part of the abdomen for twelve months suggestive of a peptic ulcer, and six months prior to the meeting a barium meal X-ray examination showed evidence of a duodenal ulcer. He was in his usual health till some fourteen hours prior to his admission to hospital, when he experienced a sudden severe upper abdominal pain accompanied by vomiting. He was admitted to the Saint George Hospital with the diagnosis of a perforated peptic ulcer.

On examination the patient was in obvious distress. He had board-like rigidity over the whole abdomen, but the greatest tenderness was just above the umbilicus. His temperature was 100° F. and his pulse rate 80 per minute. At operation, through a right upper paramedian incision, much free fluid was found in the abdomen. The stomach and duodenum were normal, but about twelve inches down from the duodeno-jejunal junction a constriction of the jejunum was noted with a perforation above it. The affected segment of jejunum (six inches) was resected together with a wide wedge of the mesentery, as the affected glands were enlarged and hard. An end-to-end anastomosis was performed. A small nodule in the liver, about half an inch in diameter, was also excised. His subsequent progress was reasonably uneventful, and he was discharged from hospital in two weeks for further convalescence. Dr. Gatenby's report on the specimen was as follows: "A piece of small bowel six inches long, showing an ulcer in its mid-length encircling and constricting the bowel and perforating at one point. Sections show the ulcer to be an adenocarcinoma. The nodule resected from the liver is a secondary deposit." Dr. Pullen said that the patient was shown because adenocarcinoma of the jejunum was an uncommon condition.

### Extradural Hæmorrhage.

Dr. Pullen finally showed a female child, aged nine years, who presented a typical case of extradural hæmorrhage, as some thirty-six hours had elapsed between the time of her injury and the time of operation. The patient fell off her bicycle about 11 a.m. on September 27, 1953, and was found unconscious. She recovered consciousness in about half an hour, but commenced to vomit and was very irritable. On her admission to hospital about four and a half hours after the injury the child presented a typical picture of cerebral irritation and showed some slight neck stiffness. The pupils were equal and reacted to light. The pulse rate was 60 per minute and the blood pressure 130 millimetres of mercury, systolic, and 80 millimetres, diastolic. An X-ray examination of the skull revealed a fracture without depression of the right parietal bone extending into the base.

The patient remained at the same level of consciousness (very irritable) for twenty-four hours, when it was noted that she could be roused only with difficulty. At 5 p.m. on September 28 the child could not be fully roused, and she had an "upgoing toe" on the left side with left ankle clonus. This was followed by a generalized convulsive seizure with the right pupil a little larger than the left, but reacting briskly to light. Some five hours later (10 p.m.) the child had Cheyne-Stokes respiration, an irregular pulse, and a systolic blood pressure varying up to 140 millimetres of mercury; the right pupil was enlarged and fixed and the left pupil small and reacting.

Some of the delay at this stage was due to difficulty in locating the child's parents to obtain permission for a craniotomy. At 10.30 p.m. a burr hole was made over the fracture line in the right temporal fossa. A reasonable amount of blood clot and some fresh blood were evacuated and hæmostasis was secured. The clot extended into the base of the skull, and this necessitated enlarging the burr hole downwards and backwards. The middle meningeal artery was secured with a stitch. The *dura mater* quickly came into contact with the skull and pulsated. The child recovered on the transfusion of one pint of blood. At the end of the operation the pulse rate was 120 per minute and the systolic blood pressure was 110 millimetres of mercury.

After operation the patient caused anxiety for about twelve hours, but in forty-eight hours was fully conscious but noisy. The right pupil remained much larger than the left for four days, and the pupils were not quite equal on her discharge from hospital twelve days later. The plantar reflexes were extensor in character for several days, but were flexor on her discharge. Subsequently the patient made a rapid recovery, and at the time of the meeting was back to her usual health.

Dr. Pullen said that an unusual feature was the delay of thirty-six hours before operation. It would appear that bleeding recurred after a twenty-four hours' delay, and that emphasized the maxim that a patient was more likely to benefit from surgery if his level of consciousness suddenly deteriorated after a period of stability.

### Cup Arthroplasty.

DR. A. L. WEBB showed five patients to illustrate varying phases of recovery after vitallium mould arthroplasty for osteoarthritic changes in the hip joint. He said that the end results of the earlier series justified the continuance of the operation.

### Judet's Arthroplasty.

Dr. Webb next showed a female patient who had undergone a resection reconstruction operation for a recent fracture of the neck of the femur. The head of the femur had been removed from the acetabulum and an acrylic prosthesis inserted. The operation was used for patients in the older age group. After having been in bed for three weeks the patient under discussion was up and walking with no apparent disability. The operation had been performed ten months previously.

### Polyostotic Fibrous Dysplasia.

Dr. Webb finally showed a male patient, who had been first treated at the age of three years for a fracture of the

left tibia and fibula caused by his being knocked over by a bicycle. Normal union had occurred, and no pathological changes were found on X-ray examination. Eight years later, after he had been limping and complaining of pain in the left groin for several months, physical examination revealed some limitation of movement of the left hip and wasting of the thigh. An X-ray examination revealed extensive fibrocystic changes in the upper part of the shaft, the great trochanter and the neck of the left femur. At operation complete removal of the soft, cheesy contents of cyst cavities was carried out; this operation was followed in a fortnight by attempts to fill the cavities with bone grafts from the tibia. Further radiological examination revealed a cyst in the mid-shaft of the left tibia, and areas of increased density in the upper halves of the shafts of both ulnæ with no cyst formation. Histological examination of the material removed from the femur revealed a sheet of young fibrous tissue with occasional young blood vessels; normal-looking cartilage was also found.

Six months after the grafting operation the patient walked normally, and radiological examination revealed bone regeneration in the grafted areas. Fifteen months after operation the graft was completely absorbed and the patient complained of slight pain in the thigh. In the following year there occurred a painless subtrochanteric fracture of the left femur, which united firmly in four months. The patient wore a walking caliper for about one year after that. Before the fracture of the femur, the blood calcium content estimated on two occasions was 11 and 10 milligrammes per 100 millilitres respectively, the blood phosphorus content was 2·9 and 3·1 milligrammes per 100 millilitres, and the phosphatase content was 2·2 units per 100 millilitres. Just after the fracture the blood calcium content was 12 milligrammes per 100 millilitres (normal, 9·5 to 10·5 milligrammes per 100 millilitres) and the blood phosphorus content was 4·7 milligrammes per 100 millilitres (normal, 3·2 to 4·3 milligrammes per 100 millilitres). In the femur there were now large cysts extending into the neck from the fracture site, with considerable calcification, and cysts were present in the lower end of the shaft of the femur as well as in the upper end of the tibial shaft. A pronounced deformity of the neck of the femur was present. Dr. Webb said that in spite of the extraordinary appearance of the femur, the youth, now aged eighteen years, followed all sorts of activities, and with a built-up shoe walked with only a slightly perceptible limp.

### Tuberculosis of the Hip.

DR. C. P. HUDSON showed a female patient, aged seven years, who had been admitted to hospital on July 25, 1953, with the complaint of pain in the right hip of two years' duration; the pain was more severe after exercise. The child slept with the hip flexed. No abnormality was detected in any other systems. The patient's grandmother had died from tuberculosis two years previously, and one sister had a primary focus in a lung. The mother and father were alive and well.

On examination, the patient appeared a healthy child of her stated age. The muscles of her right leg were wasted, and there was painful limitation of movement in all directions. X-ray examination of the right hip revealed what appeared to be infective arthritis of the joint; the joint space was increased and hazy, the margins of the acetabulum and of the femoral head were ill-defined, and the whole of the head and neck of the femur were rarefied. A blood count gave the following information: the hæmoglobin value was 95%; the leucocytes numbered 7000 per cubic millimetre, 64% being neutrophile cells, 24% lymphocytes, 9% monocytes and 3% eosinophile cells. The erythrocyte sedimentation rate was nine millimetres in one hour and 24 millimetres in two hours. The Mantoux test produced a strongly positive reaction. The provisional diagnosis of tuberculosis of the hip was made.

Immobilization in a Jones abduction frame was instituted. On September 8 treatment was begun with streptomycin, 0·5 gramme per day, and PAS, two tablets every four hours. On September 25 the administration of isonicotinic acid, 50 milligrammes per day, was begun. On October 9 synovectomy of the right hip was performed. After the operation immobilization was maintained on a Jones abduction frame for four days, and after that by the Hamilton Russell method with active movements. Chemotherapy was continued until October 30, when signs of toxicity appeared; it was then stopped. During the post-operative period the patient had painless movement of the joint. On November 30, when traction was discontinued, there was some pain on flexion of the hip and traction was reapplied.

### Osteotomy for Deformity of Femur following Osteomyelitis.

DR. C. M. MAXWELL showed a boy who had been admitted to the hospital on December 16, 1947, at the age of nine years. He had knocked his left knee four weeks previously, and presented with a history of pain in the left thigh and hip of nine days' duration. He had had night starts. His left hip was abducted and flexed, and severe pain was felt on abduction and extension. The hip was tender. A provisional diagnosis of acute arthritis was made. On the child's admission to hospital an X-ray examination revealed no abnormality. On December 31, 1947, an X-ray examination revealed osteoporosis of the femoral head and the adjacent part of the acetabulum. Tuberculosis of the hip was excluded by the negative response to the Mantoux test and the negative result of attempted culture of material from the joint space.

The condition was rapidly progressive, and bone destruction was obvious in X-ray films taken on February 18, 1948. In spite of the application of a hip spica, his left hip became dislocated, and on April 7 there was X-ray evidence of sequestration from the affected femoral head and erosion of the acetabulum. The dislocation was reduced by the application of Thomas splints to both lower limbs. When his condition improved, a hip spica was applied, and after his convalescence he was discharged to the out-patient department on October 22.

The child returned to hospital on April 22, 1949, with a green-stick fracture of the lower third of the right femur. This quickly healed with conservative treatment. He attended the orthopædic out-patient department, and his readmission to hospital was advised because of the presence of two inches of shortening of the left leg.

On his readmission to hospital on August 25, 1953, he had an ankylosed painless hip with two inches of shortening of the left leg. On August 26 a subtrochanteric abduction osteotomy of the left femur was performed. A hip spica was applied, and his convalescence was uneventful. At the time of the meeting his weight-bearing line was excellent.

### Cyclical Bleeding following Total Hysterectomy.

DR. SYDNEY HING showed a female patient, aged forty-one years, who had complained of abdominal swelling and pains present intermittently in the right groin for eighteen months. Her menstrual periods had been regular, with twenty-eight day cycles, and each period lasted from five to seven days. The loss was moderate and she had no dysmenorrhœa, but a definite *Mittelschmerz* was present. She was the mother of three living children and had no history of miscarriages or of any operations. Examination of the patient revealed a large symmetrical abdominal swelling, firm, not tender, and extending above the umbilicus from the pelvis. The diagnosis of *fibromyoma uteri* was made and surgical intervention was recommended to the patient.

In March, 1952, routine total hysterectomy was performed. The uterus was removed *in toto*, including the whole of the cervix, but the ovaries were conserved. The convalescence was uneventful, and in due course the patient was discharged from hospital. She returned in April for the "follow-up" examination, and complained that she had had a vaginal loss of bright red blood lasting for three days. Examination failed to reveal any cause for the bleeding. The abdominal wound was soundly healed and the vaginal vault in a satisfactory condition. The patient was reassured and was told to report back if there was any further vaginal bleeding. The pathological report on the specimen submitted was as follows. Macroscopic examination of the uterus revealed several intramural fibroid tumours, the largest of which was five inches in diameter. The cavity was very small and compressed by the tumours. On microscopic examination the tumours were found to be simple fibromyomata. The body of the uterus and endometrium appeared normal.

It was not until September, 1952, that the patient returned seeking treatment for a small papilloma of the left nipple. This was a source of annoyance because of bleeding brought on by trauma. However, in the course of the consultation, the patient volunteered the information that she was still having her monthly menstrual periods, which she described as being exactly like her menstrual periods prior to the operation. The cycle was twenty-one to twenty-eight days and the flow persisted for six days, although she considered that the amount was slowly diminishing. Vaginal examination again failed to reveal any signs whatever of bleeding, much less the cause of the bleeding. There was now no *Mittelschmerz* in the cycles. The patient was then asked

to keep a record of the dates of her cycles and to return after three months on a day when her "period" was at its height.

The patient returned four months later during a "period", and armed with a complete record which bore out her claims. Examination on that occasion revealed the presence of several hæmorrhagic areas scattered over the vaginal vault. The areas were dendritic in outline. Investigation of the hæmatopoietic system produced nothing of note, and the patient was advised to undergo biopsy excision of some of the hæmorrhagic areas.

In May, 1953, at a time coinciding with a "period" two of the largest of the hæmorrhagic areas were excised from the vaginal vault and examined by the pathologist, Dr. Gatenby. He reported that the specimens on macroscopic examination were seen to be two white fragments. Microscopic examination revealed small submucous hæmorrhages. The histological appearances did not suggest any particular cause. There was no evidence of any endometrial element.

The patient returned again in June, 1953, when she was told of the pathologist's report and its significance, or rather the lack of it. Examination of the vaginal vault again showed that it had healed completely. She was asked to report at intervals, and up to the time of the meeting since the biopsy excision in May no further "period" had been experienced by her.

Dr. Hing said that he was unable to offer any explanation for the case; a search of the literature had failed to enlighten him. Prior to the biopsy excision he had been convinced that the case was one of vaginal endometriosis, but the pathologist's report did not support that supposition.

### Pseudo-ovarian Ectopic Gestation.

Dr. Hing's second patient was a married woman, aged thirty-six years, who had been admitted to hospital on January 29, 1953, under his care, with the following history. On January 10, after a period of amenorrhœa lasting one month, the patient visited her doctor and presented with a complete ovum, having had a miscarriage. This was examined and considered complete and intact. The doctor sent the patient home and within three days bleeding had ceased. Two days later she went on a vacation, but after two days away she began to suffer from recurrent pain in her right side and she was treated for a "germ in her bladder". Her condition did not improve, and shortly she returned home. On January 29 she had a sudden and severe attack of abdominal pain and sent for her doctor, who had her admitted to hospital immediately with the provisional diagnosis of ruptured pelvic abscess. By the time the patient was in hospital the pain had moved from the right side to the whole of the lower part of the abdomen. Thirty minutes after the onset of the severe pain she experienced pain in the right shoulder and to a lesser extent in the left shoulder.

On examination the patient was seen to be in a state of collapse and in obvious pain. She was very pale, cold and clammy. Her temperature was subnormal, and the heart sounds were faint and rapid. The blood pressure was 75 millimetres of mercury, systolic, and 50 millimetres, diastolic. Palpation of the abdomen revealed generalized guarding with abdominal distension. Vaginal examination showed the presence of a small amount of brown discharge issuing from the *os uteri* and a tender cystic mass in the right fornix. The provisional diagnosis was considered to be ruptured tubal ectopic gestation or ruptured ovarian cyst, and arrangements were made for immediate laparotomy. In the meantime a drip transfusion of blood was in progress.

When the abdomen was opened the cavity was seen to be filled with blood and blood clot. A rounded cystic mass about the size of a small orange lay on the right side. No ovary recognizable as such was seen on that side. The mass was excised, as much blood and blood clot as possible was evacuated, and the abdomen was then closed. Convalescence was uneventful and the patient was discharged from hospital, well.

Dr. Hing said that at first sight the specimen removed resembled a ruptured fimbrial cyst; but when the contents of the cyst were seen the diagnosis of ovarian ectopic pregnancy was made and not disproved until histological examinations had been completed. Ovarian pregnancy was a rarity, there having been reported in the literature no more than 50 or 60 cases which were authenticated and conformed to the accepted criteria of diagnosis laid down by Spiegelberg in 1878. The criteria were: (i) an intact salpinx on the affected side had to be clearly separate from the ovary; (ii) the gestation sac had to occupy the normal position of the ovary; (iii) the gestation sac had to be connected to the uterus by the ovario-uterine ligament; (iv) ovarian tissue had to be demonstrable in the walls of the sac in several positions. In the case under review the Fallopian tube at first sight appeared to be intact, and the gestation sac occupied the normal position and was attached to the uterus by the ovarian ligament. However, histological examination failed to satisfy the fourth requirement. The pathologist reported that the specimen appeared to be a thin-walled ovarian cyst, two and a half inches in diameter, with a small portion of Fallopian tube on one side. The contents of the cyst were an amniotic sac approximately two inches in diameter, containing an embryo seven centimetres in length. On one side there was a well-formed placenta. Microscopic examination of sections taken from the cyst wall did not reveal ovarian tissue, and the relations of the ectopic tissue to the pieces of tube sectioned suggested an origin in the fimbrial end of the tube, with compression and destruction of the ovary or extension into a simple ovarian cyst.

Dr. Hing said that the case presented several interesting features. In the first place, the patient had an extrauterine and an intrauterine pregnancy *pari passu*. That in itself was a rare occurrence. The referring doctor had seen the ovum of the intrauterine pregnancy presented by the patient on miscarriage. He was certain that the ovum was intact and that it was not a uterine cast. In the second place, as was wont to happen in cases of ectopic gestation, the patient had been under investigation and treatment at the Royal Prince Alfred Hospital for sterility (Grant, at the Women's Hospital, Crown Street, reported an incidence of almost 2% in his series). In the third place, the patient in 1941 had had a twin pregnancy which she lost, and in 1944 a single pregnancy had suffered a similar fate. At the age of thirty-six years the unfortunate woman was still childless and she had but to have a second ectopic pregnancy involving her left adnexa to complete a sad tale. The recurrence rate had been estimated at a figure as high as 10% by J. Haffner in 1940.

### Multiple Calculi in the Urinary Tract.

DR. R. I. CAMPBELL showed a male patient, aged fifty-one years, who had reported to the out-patient department on June 16, 1953, with a history of having had attacks of retention of urine over the last few years. His bladder had had to be catheterized on some occasions. Over a period of about eleven years he had been having attacks of "pyelitis", by which he meant scalding with micturition and passing of gravel. Nine years previously he had had a stone crushed in his bladder.

On examination of the patient, no abnormality was palpable in either loin, nor was any abnormality detectable on rectal examination. His urine was grossly infected. An X-ray examination on June 18 revealed a large staghorn calculus in the right kidney, an elongated calculus in the lower end of the left ureter, and a rounded calculus in the bladder. A culture of his urine produced a growth of *Staphylococcus aureus*. On August 1 a cystoscopic examination was carried out. The calculus was noted in the bladder. A ureteric catheter became blocked four centimetres from the left ureteric orifice. This orifice was then slit with a diathermy electrode. It was also noted that indigo-carmine was secreted in fair concentration from the right ureter. A few days later the patient passed the ureteric stone. On August 6 an excretion pyelogram revealed severe hydronephrosis of the left kidney. On August 8 the stone in the bladder was removed by litholapaxy.

The patient was discharged from hospital on August 11, and arrangements were made for a further excretion pyelographic examination in three months. It was thought that in that time the left kidney would recover and he would be fit for nephrectomy of the right kidney.

On October 22 a further excretion pyelographic examination was made and the change in the left kidney was remarkable. The dye appeared almost immediately after the injection, and there was no evidence of hydronephrosis. The function of the patient's left kidney was excellent at the time of the meeting and he was awaiting admission to hospital for the removal of his right kidney with its staghorn calculus.

# Out of the Past.

*In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.*

## FROM THE LORDS OF THE ADMIRALTY TO LIEUT. JAMES COOK.[1]

[From "The Historical Records of New South Wales".]

30 July, 1768.

WHEREAS there is a great reason to believe, from what Dr. MacBride has recommended in his book entitled "Experimental Essays on Scurvy and other Subjects" and his pamphlet entitled "An Historical Account of the New Method of Treating the Scurvy at Sea" (of which you will herewith receive copies) and from the opinion of other persons acquainted with scorbutic disorders that malt made into wort may be of great benefit to seamen in scorbutic and other putrid diseases: and whereas we think fit experiments should be made of the good effects of it in your present intended voyage and have with that view directed the Commissioners of the Victualling to put a quantity on board the bark you command: you are hereby required and directed to cause the same to be stowed in the bread room or some very dry part of the ship, and take care that the following rules with respect to the preparation of the said wort, the administration of it to the sick etc. be in general observed viz.

I. The malt must be ground under the direction of the surgeon and made into wort (fresh every day especially in hot weather) in the following manner viz. Take one quart of ground malt and pour on it three quarts of boiling water, stir them well and let the nurture stand close covered up for three or four hours, after which strain off the liquor.

II. The wort so prepared is then to be boiled into a panada[2] with sea biscuit or dried fruits usually carried to sea.

III. The patient must make at least two meals a day on the said panada and should drink a quart or more of the fresh infusion, as it may agree with him, every twenty-four hours.

IV. The surgeon is to keep an exact journal of the effects of the wort in scorbutic and other putrid diseases not attended with pestilential symptoms carefully and particularly noting down, previous to its administration, the cases in which it is given, describing the several symptoms and relating the progress and effects from time to time which journal is to be transmitted to us at the end of the voyage.[3]

Given under our hands this 30th July 1768.

ED. HAWKE.
PERCY BRETT.
C. SPENCER.

[1] From the original in the Mitchell Library, Sydney.

[2] Bread boiled to a pulp and flavoured.

[3] The report required by the Lords of the Admiralty was furnished by Surgeon William Perry, who had been promoted from Surgeon Mate on the death at Batavia on November 5, 1770, of Surgeon William Brougham Monkhouse. Cook sent it on under date July 12, 1771. Perry reported that in the early part of the voyage wort was not used owing to the ready availability of other foodstuffs with presumed antiscorbutic properties. These included sauerkraut, mustard, vinegar, wheat, inspissated orange, lemon juices, saloup, portable soup, sugar, molasses and sundry vegetables. Issues of salt meat were reduced, butter and cheese were removed from the dietary scale and frequent cold bathing was enforced. After the ship crossed the equator some members of the ship's company were affected by a "bilious disorder", and to these for a time a quart of wort was issued daily as well as to the cooks, "who were supposed more obnoxious to scurvy from duty about the fire". Early in 1769 a few members of the crew suffered from scurvy and the issue of wort was resumed. It remained part of the ship's company's diet thereafter whilst they were at sea, and during the remainder of the voyage there were only five cases of scurvy, the patients being successfully treated with lemon juice. Perry sums up as follows: "It is impossible for me to say what was most conducive to our preservation from scurvy, so many being the preventives used, but from what I have seen the wort perform, from its mode of operation, from Mr. McBride's reasoning, I shall not hesitate a moment to declare my opinion viz.—that the malt is the best medicine I know, the inspissated orange and lemon juices not even excepted."

# Correspondence.

## BRONCHIECTASIS WITH NORMAL PLAIN X-RAY FINDINGS.

SIR: In reply to several letters in reference to my paper on "Bronchiectasis with Normal Plain X-Ray Findings" I would like to thank Dr. Rennie and Dr. Maitland for their agreement with remarks set out in my paper.

Dr. Cotter Harvey says that he may be provocative. He suggests that the radiological technique and interpretation are at a low ebb in the areas from which my cases have been drawn. Thirteen cases came from 12 widely scattered suburbs and 12 from 11 widely separated country towns. Moreover, they were not rayed in their own districts alone, some being rayed in a number of places while seeking treatment over the years. Twelve of the final plain rays were taken and reported on by competent radiologists, seven of these by the radiologist who I heard Dr. Harvey state at a recent meeting took most of his private rays. The other 13 had rays taken at public hospitals, three in widely separated country districts and ten at four city hospitals, seven being taken at one of the main hospitals at which Dr. Harvey works.

In my paper I laid no blame at the door of the radiologist. In fact, one of them opened the discussion on my paper, drawing particular attention to this point in his preliminary remarks.

Dr. Harvey mentions the minor changes which Wynn Williams recently called attention to, stating that they may be missed in the plain ray. This is, of course, the basis of my whole paper; when I say that if these rays are returned as or appear normal, then the history and clinical findings demand an early bronchogram.

My paper had to be condensed into the limited time allowed me, and the number of diagrams I was permitted to publish in the article was also limited. This prevented me showing other views which were naturally taken and which Dr. Harvey would like to have seen. Still, those published show the lesions mentioned, and one is an oblique view, which apparently escaped Dr. Harvey's notice. He states that the films shown are antero-posterior exposures, but surely it would be more "in line with modern concepts" if he called them postero-anterior exposures.

I would like to quote a further case here with a somewhat similar story. Recently a patient, aged eighteen years, was called up for service in the army. Plain X rays were taken, and after he was examined he was passed as fit. He mentioned that he had bronchiectasis, and more rays were taken and he was again passed as fit. He then sought a certificate from me and later the authorities rang me up. When I told them that he had a marked atelectasis of the left lower lobe, which was also bronchiectatic, as well as having bronchiectasis of the lingula and right middle and lower lobes, it was decided not to call him up for service.

Yours, etc.,

229 Macquarie Street,
Sydney,
April 28, 1954.

H. B. HARWOOD.

## CORTISONE AND ACUTE RHEUMATISM.

SIR: I was very interested in Dr. Meyers's letter of April 17 on the clinical use of cortisone in rheumatic diseases. I would like to add some details of dosage and treatment which I hope will be useful.

While visiting arthritic centres in the United States of America in December, 1953, at the Mayo Clinic I discussed at length with Dr. Philip Hench and Dr. Slocumb their present dosage of cortisone, and the complications encountered. Dr. Hench and Dr. Ward have recently written a chapter for a new book, as yet unpublished. They kindly allowed me to summarize this chapter, and gave me permission to pass on the details in this country. It is as follows.

*Policies in Dosage.*—Give enough to provide noteworthy relief without significant side effects.

*Components of a Dose Scheme.*—A dose scheme is made up of (i) priming doses, (ii) suppressive doses, (iii) dose reduction, and (iv) maintenance dosage.

*Present Dosage Scheme.*—The initial suppressive dose is 40 to 75 milligrammes for men, 20 to 35 milligrammes for

women in the post-menopausal stage, 30 to 50 milligrammes for other women, and 15 to 30 milligrammes for children. As soon as the response is definite, reduce the dose; this should be within a week. The decrements are: 5·0 to 12·5 milligrammes daily if the dose is more than 50 milligrammes; 2·5 to 5·0 milligrammes if the dose is 50 milligrammes or less. The period varies with the response; if considerable reduction has been well tolerated, make a further reduction in two to seven days.

The maximum daily dosage should not exceed 65 milligrammes for men, 35 milligrammes for women in the post-menopausal stage, 35 milligrammes for other women, and 25 milligrammes for children. If the temperature increases in flare or stress, add 5·0 milligrammes daily if it is mild, 10 milligrammes daily if it is severe.

If surgical treatment becomes necessary in those who have had cortisone in the past six months to two years, give 200 milligrammes of cortisone intramuscularly forty-eight hours, twenty-four hours and two hours before operation. On the day after operation give 100 milligrammes intramuscularly. During the next two or three days gradually reduce the dosage to pre-operative level, continuing intramuscular administration. On the fifth day after operation change to oral administration.

If urgent surgery is necessary, give 200 milligrammes intramuscularly as soon as possible and again immediately before operation. During operation give 100 milligrammes intravenously in normal saline and glucose (5%) solution. After operation the routine is as before.

*Hypercortisonism.*—Hypercortisonism is a very definite clinical entity. It is most frequently met with in women in the post-menopausal stage, but can occur in any patients having cortisone medication. The symptoms are; (i) excessive fatigability and weakness; (ii) aching in muscles and joints, often diffuse with loss of movement; (iii) emotional instability with (*a*) loss of sense of time and (*b*) gradual withdrawal from society. The signs are: (i) increased erythrocyte sedimentation rate, which may be due to progressive hypercortisonism and must be distinguished from (*a*) significant overdosage, (*b*) the presence of some complication, major or minor, and (*c*) any of the situations related to "flares" (it is interesting to note that the erythrocyte sedimentation rate is not increased in Cushing's syndrome); (ii) great shortening of the coagulation time of the blood, leading to thrombo-embolic phenomena; (iii) osteoporosis of the skeleton, especially the vertebral bodies. The treatment is reduction of dosage of the cortisone in a step-wise manner and alternation with ACTH.

The supplies of cortisone in the United States of America have been very liberal in spite of the high cost, and therefore the complications of high dosage over a prolonged period are becoming manifest. They are very real and very worrying, and must be avoided.

Yours, etc.,

143 Macquarie Street, Sydney,
April 22, 1954.

M. NAOMI WING.

## REGISTRATION OF MEDICAL PRACTITIONERS IN NEW SOUTH WALES.

SIR: Surely some move can be made to oppose the annual registration fee, due to be enforced next month. Time is short—failing swift action this impost will be firmly established. Is it to succeed in default of any organized resistance? Not only is a very important principle involved; it is quite possible that this annual tax will grow with the years.

Yours, etc.,

43 Cammeray Road, Cammeray,
New South Wales.
May 16, 1954.

D. S. LEITCH.

## THE USE OF MUSCLE RELAXANTS IN ELECTRO-CONVULSIVE THERAPY.

SIR: The opinion at the Brisbane Mental Hospital on the administration of electro-convulsive therapy with "Brevidil" differs from that expressed by Dr. E. F. Fletcher in the journal on April 17, 1954. We have followed the advice of Dr. R. Webb (M. J. AUSTRALIA, April 11, 1953) and employed the simplest technique possible.

1. No atropine premedication is given, and no avoidable side effects resulted from the omission.

2. No "Pentothal" is given preceding the "Brevidil" injection, as it adds to the risk of the procedure, is time-consuming, and is unnecessary. On questioning, only one of our patients complained of any unpleasant sensation following the "Brevidil" injection, and it was not sufficiently marked to frighten him of further treatment. In the majority, retrograde amnesia due to electro-convulsive therapy prevented them from remembering having an injection.

3. In view of the simplicity of technique and minimal risk of any side effects, we fail to see that it is necessary to have an experienced anæsthetist administer the treatment.

Yours, etc.,

Brisbane Mental Hospital, Goodna, Queensland.
April 21, 1954.

N. E. PARKER.

# University Intelligence.

## THE UNIVERSITY OF SYDNEY.

AT a ceremony held in the Great Hall of the University of Sydney on Wednesday, May 5, 1954, the degree of Doctor of Science *honoris causa* was conferred on Sir John Percival Vissing Madsen, Emeritus Professor of Electrical Engineering, by the Chancellor, Sir Charles Bickerton Blackburn.

The formal presentation of the recipient for the degree was made by the Deputy Chancellor, Dr. C. G. McDonald.

Dr. McDonald spoke as follows:

Mr. Chancellor,

The conferring of an honorary degree on a man of distinction is always a happy occasion, but when the recipient is an alumnus of the university which grants it, the honour falls on him with greater grace, for the university, though a loving mother, demands the most rigid standards of achievement from her own children.

John Percival Vissing Madsen is one of the best scholars this university has produced. Mathematician, physicist, engineer, he won the university medal for mathematics in his science course and another university medal cn graduation in engineering. In 1920 he was appointed Peter Nicol Russell Professor of Electrical Engineering and after some twenty years of professorial service he became Dean of his faculty and a Fellow of the Senate. From 1947 till his retirement he was Chairman of the Professorial Board, the highest academic post of any serving professor.

Whereas some great scholars exercise all their influence within the cloisters of the university, allowing their students after graduation to disseminate their learning vicariously, this is not true of John Madsen. If we could use an intellectual Geiger counter we should find evidence of his activity in every corner of the Commonwealth. When in the early days of radio boys of all ages were convinced that the strange noises issuing from their crystal sets came from China or Russia, it was John Madsen who determined to explore the atmosphere and the ionosphere in an attempt to increase our knowledge of the propagation of radio waves. To this end he founded the Radio Research Board of Australia, a body whose record of fundamental scientific investigation is not inferior to that of similar bodies in the United Kingdom and in the United States of America.

The next great chapter in his life was his association with Australia's contribution to research into radar, that discovery which perhaps more than any other decided victory for the Allied forces in the second World War. Appointed chairman of the advisory committee of the Radiophysics Laboratory of the Council for Scientific and Industrial Research, he with his large team of young scientists poured into the pool of radar investigation Australia's goodly share of fundamental and applied research.

Many other achievements lie to his credit. It is enough to mention the formation of the National Standards Laboratory, his work on the Council for Scientific and Industrial Research, his chairmanship of the Australian National Research Council, and his chairmanship of the Electrical Research Board of the Commonwealth Scientific and Industrial Research Organization. Already in 1941 he had been honoured by his King with the order of knighthood.

In these exciting and dangerous times when, almost literally, we see men of science

> Rift the hills, and roll the waters,
> flash the lightnings, weigh the Sun,

is it any wonder that this university should wish to honour one who has brought to her much honour by his offerings to science?

Mr. Chancellor, I present Sir John Percival Vissing Madsen, Knight, Doctor of Science, Bachelor of Engineering, Fellow of the Institute of Physics, Member of The Institution of Engineers, Australia, for admission to the degree of Doctor of Science, *honoris causa*.

# Public Health.

## INFECTIOUS DISEASES IN QUEENSLAND.

THE following notice has appeared in the *Queensland Government Gazette*, Number 2, of May 1, 1954:

His Excellency the Governor, with the advice of the Executive Council, has, in pursuance of the provisions of *The Health Acts*, 1937 to 1949, declared the disease known as "Anthrax" to be an infectious disease under the said Acts with respect to the whole of the State of Queensland.

W. M. MOORE.

## THE POLIOMYELITIS SOCIETY.

THE following statement is published for the information of the medical profession at the request of the Poliomyelitis Society (New South Wales).

The Poliomyelitis Society was founded in August, 1951, at the height of the poliomyelitis epidemic then raging. Registration as a charitable organization, however, was not granted until October, 1951. In December of that year the Lord Mayor, the Honourable E. C. O'Dea, M.L.C., officially launched the Society at a meeting of representative citizens at the Sydney Town Hill.

In December, 1952, the Society became an incorporated body. Its aims were: (i) the after-care of persons suffering from poliomyelitis; (ii) the supply of (*a*) equipment such as wheel-chairs, calipers, hospital beds, special mattresses and crutches, and (*b*) equipment for rehabilitation, such as typewriters, "Tait" hand-controls for cars, and correspondence courses in typewriting, shorthand and book-keeping *et cetera*; (iii) the subsidizing of research now being carried on at the Institute of Epidemiology at Prince Henry Hospital.

In regard to the first aim of after-care, "Cherrywood" at Turramurra was acquired. It took many months to equip and furnish it for occupation, and the first patients were admitted on July 4, 1953. The types of patient taken are in two categories: (i) the badly incapacitated patients needing extensive after-care treatment; (ii) the patient who is cared for at home and is admitted for a short-term holiday period to permit the parents to have a rest from the arduous care of nursing. The Society, although registered to care for patients of all ages, concentrates on those in the adolescent and adult age groups, as the children are well cared for by the Crippled Children's Society and the Far West Scheme.

The second aim of supplying equipment has fulfilled a great need. All equipment is on loan, but can be retained for as long as it is needed. Altogether 170 persons have been assisted in this manner in the last year, and a large number have been assisted with practical aid, such as consultations with the Society's medical panel and voluntary transport.

To date the Society has not had funds available to subsidize research.

In May last year the Society acquired a large water-frontage property at Kirribilli, to be used for a fourfold purpose: (i) For accommodation of country patients needing specialist consultations and being fitted with calipers *et cetera*. (ii) For the Fellowship headquarters, in which they can have film evenings and entertainments in the ballroom and reception rooms. As soon as the hydrotherapy pool is constructed the poliomyelitis patients will be able to bathe in privacy, which is not afforded elsewhere but is important to persons who are physically handicapped. Fellowship

**DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED MAY 8, 1954.[1]**

| Disease. | New South Wales. | Victoria. | Queensland. | South Australia. | Western Australia. | Tasmania. | Northern Territory. | Australian Capital Territory. | Australia. |
|---|---|---|---|---|---|---|---|---|---|
| Acute Rheumatism | 3(2) | 4(1) | 1 | .. | 1(1) | .. | .. | . | 9 |
| Amœbiasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Ancylostomiasis | .. | .. | .. | .. | .. | .. | 1 | .. | 1 |
| Anthrax | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Bilharziasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Brucellosis | .. | 1 | .. | .. | .. | .. | .. | .. | 1 |
| Cholera | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Chorea (St. Vitus) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Dengue | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Diarrhœa (Infantile) | 9(5) | 15(14) | 4(4) | .. | .. | .. | 2 | .. | 30 |
| Diphtheria | 15(11) | 1 | 3(3) | .. | 2(2) | .. | .. | 1 | 22 |
| Dysentery (Bacillary) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Encephalitis | 1 | .. | .. | .. | .. | .. | .. | .. | 1 |
| Filariasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Homologous Serum Jaundice | .. | .. | .. | .. | .. | 1(1) | .. | .. | 1 |
| Hydatid | .. | .. | .. | .. | 1(1) | .. | .. | .. | 34 |
| Infective Hepatitis | 18(4) | 15(7) | .. | .. | .. | .. | .. | .. | 3 |
| Lead Poisoning | .. | 3(3) | .. | .. | .. | .. | .. | .. | .. |
| Leprosy | .. | .. | .. | .. | .. | .. | .. | .. | 5 |
| Leptospirosis | 2 | .. | 3 | .. | .. | .. | .. | .. | 1 |
| Malaria | .. | .. | 1(1) | .. | .. | .. | .. | .. | 5 |
| Meningococcal Infection | .. | 3(2) | .. | .. | 1 | 1 | .. | .. | .. |
| Ophthalmia | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Ornithosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Paratyphoid | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Plague | .. | .. | .. | .. | .. | .. | .. | .. | 44 |
| Poliomyelitis | 15(8) | 16(7) | 3(2) | 1(1) | 7(6) | .. | .. | 2 | 1 |
| Puerperal Fever | .. | .. | 1(1) | .. | .. | .. | .. | .. | 19 |
| Rubella | .. | 13(8) | 1(1) | .. | 5(4) | .. | .. | .. | 2 |
| Salmonella Infection | .. | .. | .. | .. | 2(2) | .. | .. | .. | 60 |
| Scarlet Fever | 12(5) | 40(17) | 3(3) | 3 | 2(1) | .. | .. | .. | .. |
| Smallpox | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Tetanus | .. | .. | .. | .. | .. | .. | .. | .. | 6 |
| Trachoma | .. | .. | .. | .. | 6 | .. | .. | .. | .. |
| Trichinosis | .. | .. | .. | .. | .. | .. | .. | .. | 115 |
| Tuberculosis | 48(37) | 45(35) | 3 | 5(3) | 8(5) | 5(3) | 1 | .. | 2 |
| Typhoid Fever | .. | .. | .. | .. | 2(1) | .. | .. | .. | .. |
| Typhus (Flea-, Mite- and Tick-borne) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Typhus (Louse-borne) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Yellow Fever | .. | .. | .. | .. | .. | .. | .. | .. | .. |

[1] Figures in parentheses are those for the metropolitan area.

means much to the poliomyelitis patients who, without voluntary transport and the interest of a fellowship club, would perhaps be completely homebound. (iii) For the offices of the administration of the Society. (iv) For a "sheltered workshop" and a splint department, which it is hoped to establish in the basement.

At the moment the Society has five country branches. These branches are raising funds on the basis that 50% is retained in the country town itself for the use of local poliomyelitis patients and also to establish a fund, so that in an epidemic it will be possible for extra nursing and physiotherapy treatment to be made available to the afflicted. No government subsidy is received, and all funds to carry on this work have been supplied by a generous public.

## Naval, Military and Air Force.

### APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 29, of May 6, 1954.

NAVAL FORCES OF THE COMMONWEALTH.

**Permanent Naval Forces of the Commonwealth (Sea-Going Forces).**

*Termination of Appointment.*—The appointment of Neil McAlpine Baird as Surgeon Lieutenant (for Short Service) is terminated, dated 3rd December, 1953.

**Citizen Naval Forces of the Commonwealth.**

*Royal Australian Naval Reserve.*

*Appointments.*—Peter Mervyn Elliott and David Darnton Watson are appointed Surgeon Lieutenants, with seniority in rank of 30th November, 1953, and 5th January, 1954, respectively, dated 19th February, 1954, and 25th February, 1954, respectively. Ronald Antony Harrison is appointed Surgeon Lieutenant, dated 18th February, 1954.

*Promotion.*—Surgeon Lieutenant Kenneth Rothwell Barder is promoted to the rank of Surgeon Lieutenant-Commander, dated 12th February, 1954.

*Transfer to the Retired List.*—Surgeon Lieutenant-Commander Philip Neville Simons is transferred to the Retired List, dated 18th February, 1954.

## Royal Australasian College of Surgeons.

### FINAL FELLOWSHIP EXAMINATION.

THE next meeting of the Court of Examiners for the final examination for Fellowship of the Royal Australasian College of Surgeons will be held at the College in Melbourne, beginning on Friday, October 22, 1954. Candidates who desire to present themselves at this examination should apply, on the prescribed form, to the Censor-in-Chief for permission to do so on or before September 9, 1954. The appropriate forms are available from the Secretary, Royal Australasian College of Surgeons, Spring Street, Melbourne, C.1.

Candidates who have already been approved by the Censor-in-Chief but who have not yet presented for examination may present at this examination, provided they notify the Secretary of their intention to do so by September 9, 1954.

The examination fee is £21 plus exchange on cheques drawn on banks outside Melbourne, and must be paid to the Secretary by September 9, 1954.

Should a satisfactory entry be received, the examination will be conducted in the special branch of ophthalmology as well as in general surgery.

## Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Jane, Elizabeth Rae, M.B., B.S., 1953 (Univ. Sydney), Flat 2, 197 Wardell Road, Dulwich Hill, New South Wales.

The undermentioned has applied for election as a member of the Victorian Branch of the British Medical Association:

Schubert, Wilfred, M.B., B.S., 1952 (Univ. Sydney), High Street, Cobram, Victoria.

## Deaths.

THE following deaths have been announced:

GRAY.—William Robert Sutherland Gray, on May 13, 1954, at North Melbourne, Victoria.

PHILLIPS.—Albert Raphael Phillips, on May 16, 1954, at Flemington, Victoria.

## Diary for the Month.

JUNE 1.—New South Wales Branch, B.M.A.: Organization and Science Committee.
JUNE 2.—Western Australian Branch, B.M.A.: Council Meeting.
JUNE 2.—Victorian Branch, B.M.A.: Branch Meeting.
JUNE 4.—Queensland Branch, B.M.A.: General Meeting.
JUNE 8.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

## Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

*New South Wales Branch* (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

*Queensland Branch* (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

*South Australian Branch* (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

*Western Australian Branch* (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

*Tasmania*: Part-time specialist appointments for the north-west coast of Tasmania.

## Editorial Notices.

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